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for doctors and their patients

The Official Journal of the NORTH CAROLINA MEDICAL SOCIETY January 1985, Volume 46, Number 1

Common Mononeuropathies, page 7

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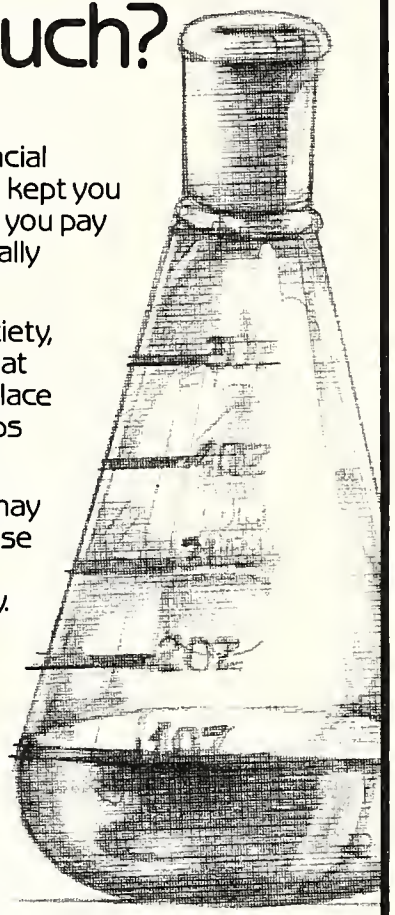
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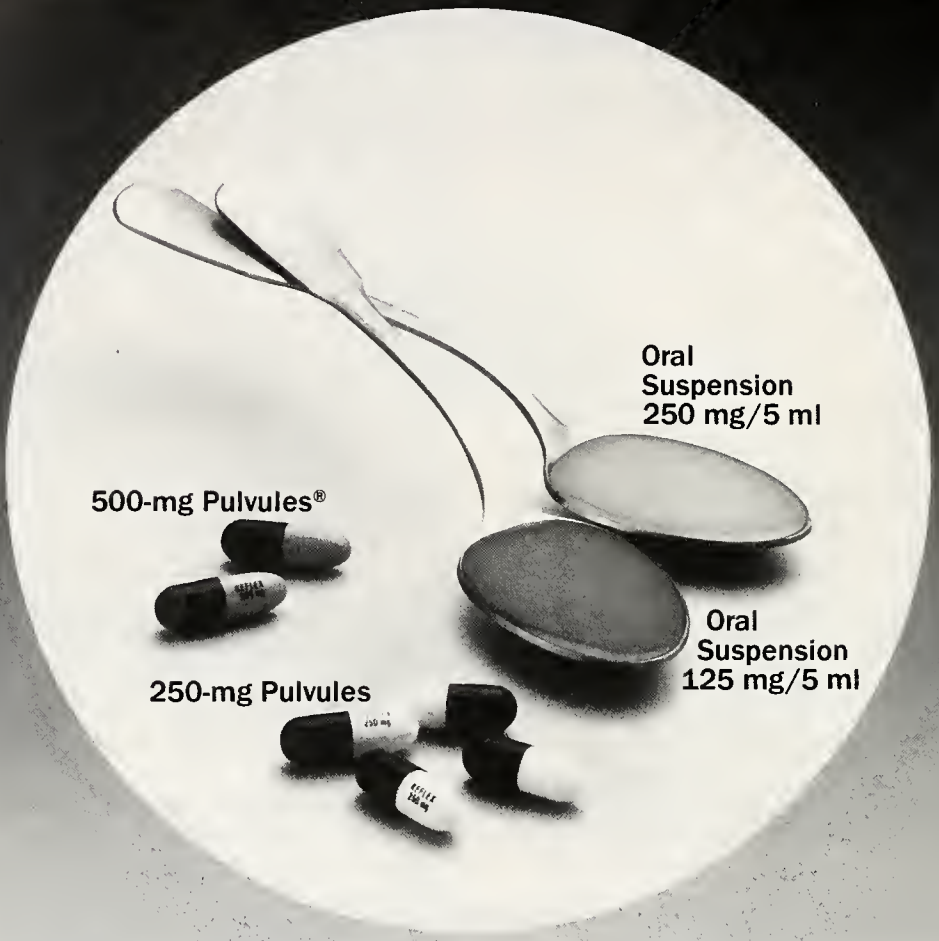
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SCIENTIFIC ARTICLE

Common Mononeuropathies

E. Wayne Massey, M.D.

• *A brief guide to the causes and cures of most common mononeuropathies.*

MOST mononeuropathies seen by physicians are "non-traumatic" in origin and due to nerve entrapment at various articulation points.

Median Nerve (Plate I)

1. Signs and Symptoms

The most common chronic mononeuropathy is the carpal tunnel syndrome (CTS). This very common neuropathy begins with intermittent numbness and tingling in the fingers, usually worse at night or when using the affected hand. The syndrome is more common in the dominant hand and symptoms are accentuated by writing, knitting, driving, bowling or similar exercise of the right hand. The diagnosis of entrapment at the wrist is often obscured by the wide distribution of pain to points distant from the site of the lesion: aching in the forearm or even shoulder which may exceed the severity of local hand symptoms. The patient loses agility and strength in the intrinsic hand muscles supplied by the distal branch of the median nerve (first and second lumbricals, abductor pollicis brevis, opponens pollicis, and the superficial belly of the flexor pollicis brevis) resulting in inability to use the hand for such tasks as opening jars or bottles. Sensory symptoms may confuse the physician because they may not be localized only to the classical median side of the hands. This may be because of the patient's inaccurate reporting, because of the sensory overlap of peripheral nerves, or because of variation in the dermatomal distribution in the median nerve.

Signs of the CTS may be subtle and only detected when the physician has a high degree of suspicion. Atrophy and weakness of the lateral thenar muscles may be signs of motor denervation (figure 1). The hand may appear bruised and have decreased autonomic function, particularly sweating. There may be decreased pain and touch perception in the first three digits and the radial surface of the fourth digit. Tinel's sign, radiation of paresthesias distally in the distribution of the median nerve with percussion over the flexor retinaculum at the wrists, and Phalen's sign, reproduction of paresthesias in the distribution of the median nerve with forced flexion of both wrists, may be helpful in diagnosis.

From the Division of Neurology, Department of Medicine, Duke University Medical Center, Durham 27710.

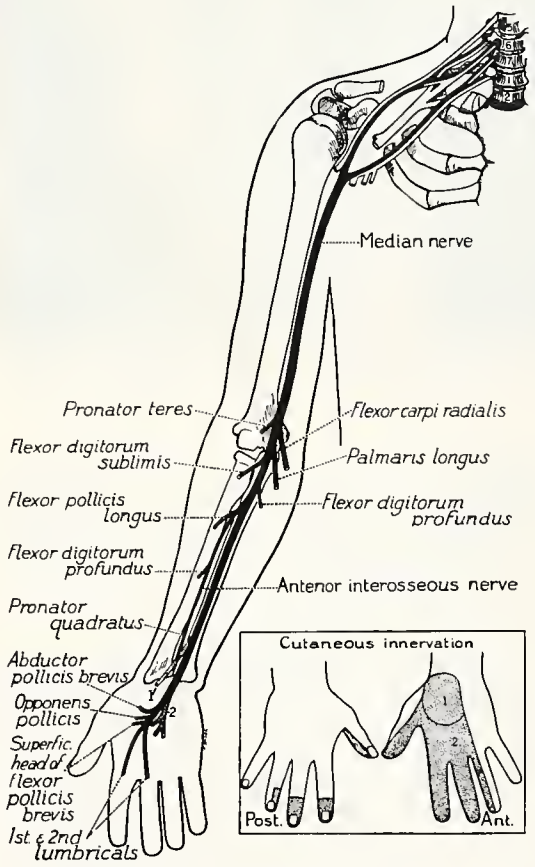


Plate I. *Median Nerve Supply*

2. Diagnostic Procedures

Nerve conduction studies demonstrating normal conduction velocities but a delay in either motor or sensory latency (or both) confirm the diagnosis of CTS at the wrist. Electromyography may demonstrate high voltage polyphasic motor units, which are the signs of chronic denervation, and fibrillations, a sign of acute denervation. In early CTS, however, the only abnormality on an electromyogram may be a diminished number of recruitable motor units.

3. Etiologies

The underlying processes responsible for CTS may include compression of the median nerve due to swelling in



Figure 1. *Median nerve entrapment underneath transverse carpal ligament; thenar muscle atrophy is present.*

the carpal tunnel caused by pregnancy,[1] rheumatoid arthritis,[2] tenosynovitis,[3] gout,[3] myxedema,[4] acromegaly,[5] diabetes mellitus,[6] trauma, or amyloid.[7] Most often, however, no specific underlying disease can be identified.

4. Other Locations for Involvement

The median nerve may be injured proximally, as it dives through the pronator teres muscle, to course distally in the forearm. In this syndrome the sensory distribution is identical to that of CTS, but the weakness includes the pronator teres, the flexor digitorum superficialis, and the section of flexor digitorum profundus to the second and third digits of the hand. The "pronator teres syndrome"[8] causes weakness of flexion of most of the digits and hand but preserves ulnar flexion and deep strength of grip supplied by the ulnar portion of flexor digitorum profundus in the powerful fourth and fifth digits.

Another injury point for the median nerve is distal to its division point under the pronator teres muscle, at the origin of the anterior interosseous branch. This deep branch may be injured while the distal superficial median nerve is unaffected so that sensation and thenar muscle strength may be preserved. Weakness occurs in the flexor digitorum profundus radialis, which affects terminal flexion of the second and third digit, and in the flexor pollicis longus which causes flexion of the tip of the thumb. This injury renders the patient unable to make a circle "O" sign in the affected hand, a movement critical for pinching activity, for grasping very small objects, and for performing many fine movements which use opposition of tips of thumb and index finger.

5. Treatment

Treatment of CTS includes a) wrist splinting using firm support to the wrist to discourage flexion/extension, b) local steroid injection under the ligament, or, most often, c) surgical section of the transverse carpal ligament.

Ulnar Nerve (Plate II)

1. Symptoms and Signs

Ulnar nerve entrapment produces numbness of the fifth finger and the ulnar surface of the fourth. Weakness of grip, opening jars, and finger spreading may be noticed since most of the intrinsic hand muscles are supplied by the ulnar nerve: all of the muscles of the hypothenar group, all of the dorsal interosseous muscles (including the large muscle between the thumb and index finger), and the third and fourth lumbricals. The greatest strength in the grip usually is supplied by the ulnar-innervated half of the flexor digitorum profundus. On examination, atrophy and weakness of the abductors and the dorsal interossei may be evident (figure 2). Palpation of the ulnar nerve in the olecranon notch may demonstrate an enlarged and easily palpable nerve (and neuroma can form in this canal).[9]

2. Etiology

Entrapment injury to the ulnar nerve is common in

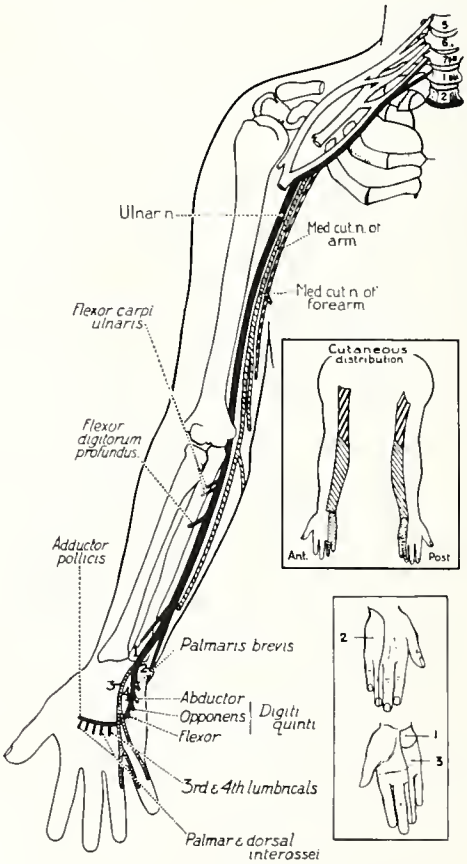


Plate II. *Ulnar Nerve Supply*



Figure 2. *Atrophy of interossei muscles due to chronic ulnar compression.*

chronic illness. Patients who are restricted to bed or a wheel chair on which they may place their elbows for support often entrap the ulnar nerve at the olecranon notch (''tardy ulnar palsy''). The immobile supine position, with the arms in a position of mild flexion and the forearm pronated, exposes the ulnar nerve to chronic pressure. Injury of the ulnar nerve can also result from occupational or athletic movements of simultaneous flexion-extension and supination-pronation movements such as holding rifles, shoveling, and throwing.

3. Diagnostic Aids

Slowing of nerve conduction velocity or drop in amplitude across the elbow supports the clinical diagnosis.

4. Other Locations

The ulnar nerve can be trapped in several other locations which cause characteristic clinical deficits.[10] A lesion low in the forearm, but still proximal to the sensory branch preserves function of the more proximal branches feeding the flexor digitorum profundus; only ulnar sensory deficit and weak intrinsic hand muscles result. When the superficial distal branch of the ulnar nerve is injured, only sensory loss in the ulnar distribution (which does not supply the forearm but only the ulnar surface of the hand) is present without motor loss; an unusual injury. The more common ''jackhammer palsy'' is caused by damage to the ramus profundus (deep branch) of the ulnar nerve in the hand. Injury to this branch in the palm, distal to origin of the sensory branch which takes off in the wrist, produces no sensory loss at all. Strength in the hypothenar muscles, abductor digiti quinti and opponens digiti quinti is intact; the only muscles affected are the third and fourth lumbricals and the dorsal interossei. Atrophy of the intrinsic hand muscles, loss of dexterity of all the fingers, inability to spread the fingers, and obvious weakness of the hand result. Nerve conduction may be normal if the evoked response is measured only in the (spared) hypothenar muscles, but if evoked response is performed from the ulnar nerve to the first dorsal interosseous, or if EMG is performed upon the interossei, the abnormality will be detectable.

5. Treatment

Avoidance of elbow pressure is the primary treatment. Flexor surface transfer of the nerve is required only when signs are severe.

Radial Nerve (Plate III)

1. Symptoms and Signs

The hallmark motor deficit of radial nerve palsy is wrist drop (figure 3). Since extension of the wrist is necessary for useful grip and finger flexion, the hand is rendered essentially useless, and it may paradoxically appear that there is weakness of finger flexions. The patient may complain of weakness in grip but when the hand is held in extension all flexor functions are normal. The position of the injury can be localized by testing the triceps muscles. If the triceps muscle and reflex are affected, the damage is more proximal, such as that occurring from crutches.

It is important to distinguish a radial nerve injury from C_7 root injury. The brachioradialis muscle ($C_{5,\ 6}$) and extensors of the wrist ($C_{7,\ 8}$) are both supplied by the radial nerve. Muscles supplied by C_5 include the deltoid and the biceps; C_6 supplies the supra- and infraspinatus as well as the biceps but none of these muscles are supplied by the radial nerve. The radial nerve from its more proximal branches supplies the triceps muscle. The brachioradialis

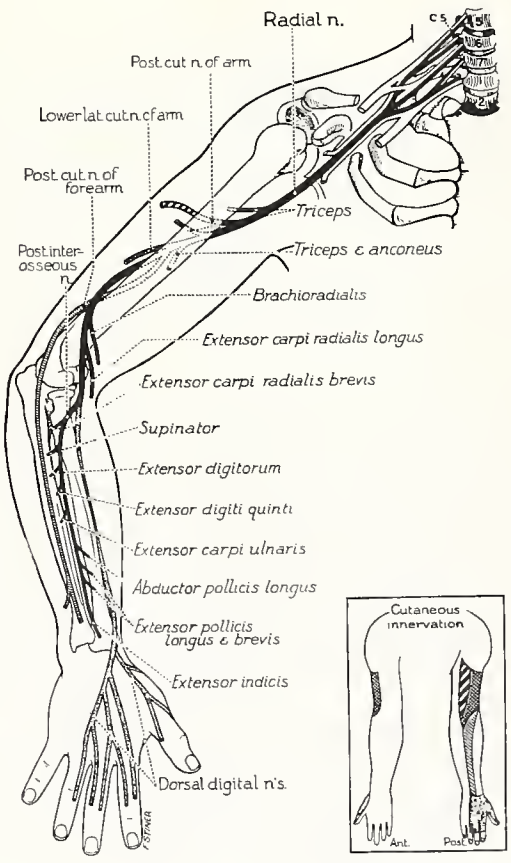


Plate III. *Radial Nerve Supply*



Figure 3. *Wrist drop from radial nerve entrapment.*

muscle ($C_{5,6}$) will be weak in a radial nerve palsy but spared in C_7 radiculopathy. This muscle is tested by evaluation of flexion of the elbow with the forearm midway between pronation and supination.

2. Diagnostic Aids

Nerve conduction velocity (NCV) of the superficial radial nerve and electromyography (EMG) of radial supplied muscles may assist when the clinical diagnosis is not clear. EMG changes begin to appear two to three weeks after the insult.

3. Etiologies

The most common site of injury of the radial nerve is in the proximal portion of the nerve as it wraps behind the humerus. This occurs while the patient is asleep or unconscious (usually due to alcohol) when the arm is held in abduction and lateral rotation against a sleeping partner lying with the head against the humerus ("honeymoon palsy"), or when the arm is propped over a bench, chair, or bar ("Saturday night palsy"). Usually there is no sensory loss, but when it occurs the involved area is the dorsal web between the thumb and the first finger.

4. Other Locations

Additional sites of radial nerve injury include the superficial sensory branch and the branch to the supinator muscles proximal and lateral in the forearm, the latter caused by: a) bursitic injury to the terminal supinator branch, or b) injury at the elbow causing distal trauma to the branch of the radial nerve supplying the muscles of supination: anconeus and the supinator. Involvement of these muscles causes weakness, and sometimes pain with pronation, and may be confused with "tennis elbow," an articular tenosynovitis. Cheiralgia paresthetica,[11] the clinical syndrome of entrapment of the distal superficial radial nerve, may occur with strictures around the wrist, such as handcuffs, or such unsuspected sources as intravenous medication infiltration from the superficial vein over the radial surface (figure 4). This syndrome is entirely sensory causing burning, tingling, and numbness in the distribution of the sensory branch of the radial nerve.



Figure 4. *Cheiralgia paresthetica due to superficial radial nerve lesion.*

5. Treatment

Treatment of radial nerve palsy consists of observation for six to eight weeks and avoidance of causative pressure. A "cockup" splint may assist hand function until it returns. Prognosis is usually good.

Lateral Femoral Cutaneous Nerve of Thigh

1. Signs and Symptoms

The lateral femoral cutaneous nerve, a sensory nerve



Figure 5. *Meralgia paresthetica from lateral cutaneous nerve injury with numbness and hyperesthesia.*

which arises from the lumbar plexus, may become entrapped at the inguinal ligament producing an acute or subacute onset of numbness and a disagreeable prickly sensation over the lateral thigh (meralgia paresthetica).[12] The disturbed sensation may be described as "burning," "pins and needles," or mere discomfort (figure 5). Surprisingly, this neuropathy is often not symptomatic and may, therefore, be detectable only by examination.

2. Diagnostic Aids

Recognition is important to avoid inappropriate intervention and to treat other conditions. Regretably, patients have been subjected to myelography and even to laminectomies for "repair" of this injury, when the anatomical deficit is clearly more peripheral. In the elderly, pelvic workup is essential since pelvic carcinoma may involve this nerve.

3. Etiology

There is a familial incidence of this neuropathy.[13] Causative factors include: standing at attention, playing sports (jogging), constrictive belts, and following surgical procedures. There is a high incidence among physicians[14] which is probably due to the simple convenience of evaluation of colleagues with this common neuropathy.

4. Treatment

Treatment, when symptoms warrant it, includes "neuropathic pain treatment" (amitriptyline, phenytoin, carbamazepine) or sometimes local nerve injection below the inguinal ligament and rarely section of the nerve.

Femoral Nerve (Plate IV)

1. Symptoms and Signs

Relatively uncommon, but devastating, is femoral neuropathy. Although usually of abrupt onset, the onset may be insidious as pain and numbness and later atrophy in the anteromedial thigh are noted. Severe weakness affects the iliopsoas and quadriceps muscles, with diminished or absent patellar reflex (figure 6).

Pain usually disappears within a few weeks, but the weakness may persist. Absence of radicular symptoms should eliminate an intervertebral "disc" diagnosis.

2. Diagnostic Aids

EMG showing acute denervation may help confirm the diagnosis. If compression of the femoral nerve by a pelvic mass is possible, CT scan of the lumbar plexus may assist in the diagnosis.

3. Etiology

Stretch of the femoral nerve may occur with leg hyperextension. In nontraumatic cases, 75 percent of patients with femoral neuropathy have diabetes mellitus. It may be the first indication of diabetes. In diabetes, the underlying cause is probably occlusion of the vasa nervorum.[15] Other etiologies include retroperitoneal mass, due to either neoplasm or hematoma (i.e., coagulopathy); periarteritis nodosa; femoral hernia; and gestational deliveries.



Figure 6. *Femoral neuropathy producing left thigh atrophy.*

4. Treatment

Treatment consists of physical therapy and pain relief.

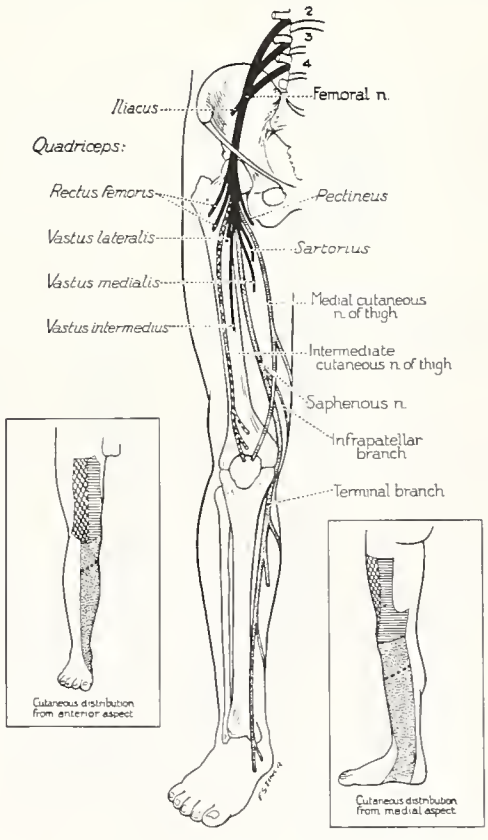


Plate IV. *Femoral Nerve Supply*

Peroneal Nerve (Plate V)

1. Symptoms and Signs

Peroneal nerve injury may cause footdrop or loss of sensation in the anterolateral surface of the foot. This can be subtle, with the only detectable sign being preferential wearing down of the anterolateral and toe portions of the shoe sole. Weakness of dorsiflexion and eversion of the foot and sensory loss in the anterolateral portion of the foot are important clinical signs. Weakness in the distribution of the peroneal nerve may be distinguished from that due to an L_5 lesion by the following observations: 1) The extensor digitorum brevis is supplied by the superficial peroneal nerve, but not the S_1 root. It may be weak (or atrophied) with peroneal nerve injury but not by L_5 root lesions. 2) The tibialis posterior muscle exerting plantar flexion and inversion of the foot is innervated by L_5 and S_1 roots but by the tibial nerve rather than the peroneal nerve.

2. Diagnostic Aids

EMG and NCV may help to determine the severity of the involvement and to distinguish peroneal from L_5 involvement.

3. Etiology

The most common inciting cause of common peroneal nerve injury is crossing the legs.[16] Observing a "dimple" sign overlying the fibular notch may give evidence of chronic leg crossing (figure 7). As with other entrapment neuropathies, immobility is a predisposing cause, and depression seems to predispose patients to peroneal

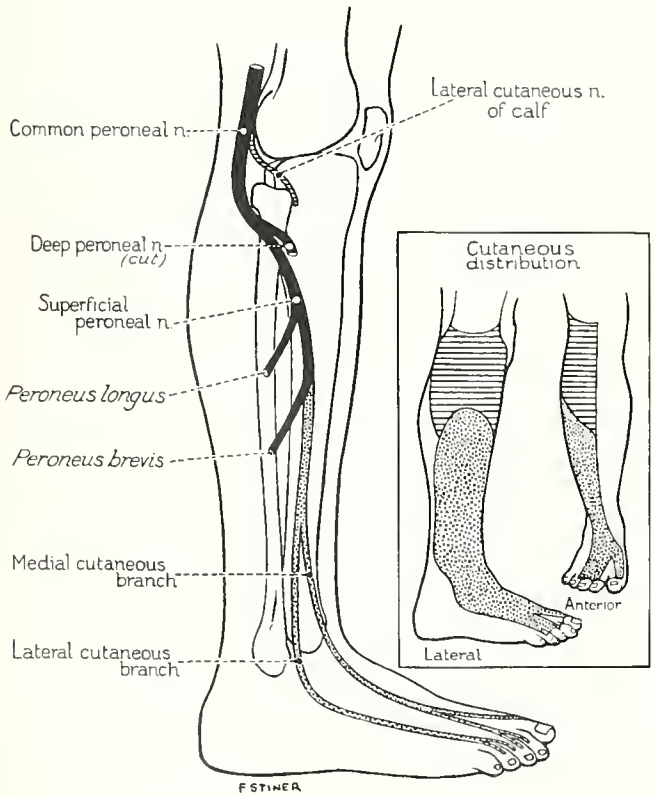


Plate V. *Peroneal Nerve Supply*



Figure 7. *Peroneal nerve palsy producing anterior compartment atrophy; note "dimple" at the fibular neck.*

neuropathy.[17] It is also seen post-stroke and in dementia. In addition to chronic leg crossing, trauma to the lateral surface of the knee, as during surgery, or trauma to the lateral surface of the leg (hence the name "running board" palsy) may produce this severe disability. Hunkering may cause this in North Carolina[18] (see cover illustration).

4. Treatment

Treatment is aimed at avoidance of leg crossing or other repetitive trauma.

Sciatic Nerve (Plate VI)

1. Symptoms and Signs

Pain on raising the legs, numbness in the foot, radiating "tingling" or pain on movement are common symptoms. In addition to accurate motor and sensory testing of the extremity, examination of the skin (Herpes lesions or evidence of trauma) and local palpation along the course of the nerve are important.

2. Diagnostic Aids

EMG and myelography or CT scanning can assist in diagnosis.

3. Etiologies

"Sciatica" is usually caused by a protruded lumbar disc

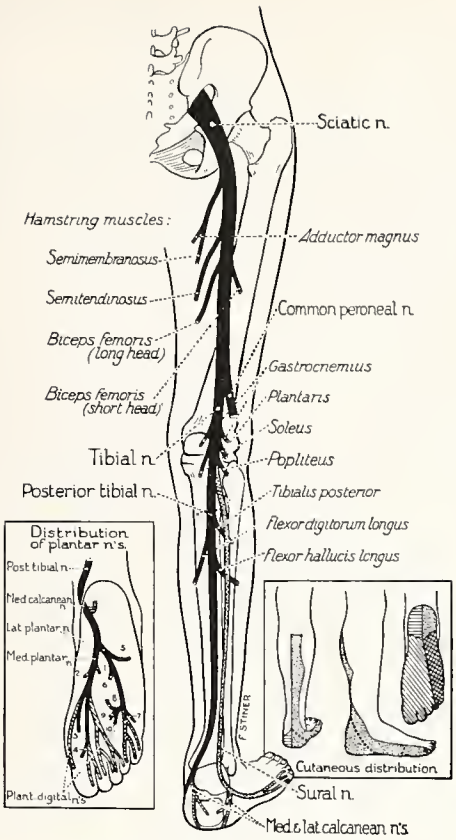


Plate VI. *Sciatic Nerve Supply*

affecting roots $L_{4,5}$ or S_1. However, the sciatic nerve is susceptible to injury at various sites in the buttocks area causing identical symptoms and signs. Local trauma to the buttocks area, such as pressure during surgery, excessive bicycle riding, wallet pressure, injections, and infections can injure the sciatic nerve in the buttocks.[19]

4. Treatment

If a disc is found by myelography it is usually removed surgically. However, conservative bed rest is often the initial therapy.

Brachial Plexus

1. Symptoms and Signs

Idiopathic inflammation of the brachial plexus (cryptogenic brachial plexopathy, Parsonage-Turner, neuralgic amyotrophy) predominantly affects the superior trunk of the brachial plexus.[20] A deep aching and pain in the axilla or shoulder is followed within a few days by weakness of muscles supplied by the superior brachial trunk, i.e., the supra- and infraspinatus, deltoid and biceps. Rhomboids, serratus anterior and other very proximal girdle muscles are sometimes involved, causing weakness of abduction and elevation of the shoulder, and weakness of external rotation (figure 8). The plexus may be affected in a spotty manner so that along with the predominant weakness of the muscles of the upper portion of the arm (Erb's palsy), muscles of the hand may also be weak.



Figure 8. *Brachial plexopathy with focal weakness producing scapular winging.*

2. Diagnostic Aids

EMG may assist in localization several weeks after the onset of symptoms. Although shoulder pain is common, bursitis or cervical root injury can be distinguished from plexus lesions by virtue of the distribution of particular shoulder muscles, involvement of the rhomboid and serratus anterior, and relative paucity of sensory findings. Cervical spine, shoulder and chest x-rays are important to eliminate local disease or fractures.

3. Etiologies

Stretching or blunt trauma from automobile accidents or motorcycle accidents are common among adults. Carrying rifles or army rucksacks may cause stretching, especially of the superior trunk of the plexus.[21] Inflammatory plexopathy may be related to infection and to immunization; many cases have occurred after large-scale inoculations in the military.

4. Treatment

Treatment includes oral steroids, if painful, and physical therapy. Prognosis is excellent (80-90% improve).

Truncal Mononeuropathy

1. Symptoms and Signs

Localized truncal sensory loss is the primary sign.

2. Etiologies

Lumbar and thoracic radiculopathy is seen most commonly due to Herpes Zoster infection. Skin lesions are almost always present.

In diabetes mellitus, diabetic truncal mononeuropathy[22] occurs and may be at multiple levels.

3. Other Locations

Localized sensory loss on the back medial to the scapula at the T2-T6 spine level occurs with notalgia paresthetica[23] (Greek notos = back). This is very common and pruritis is frequent (figure 9).

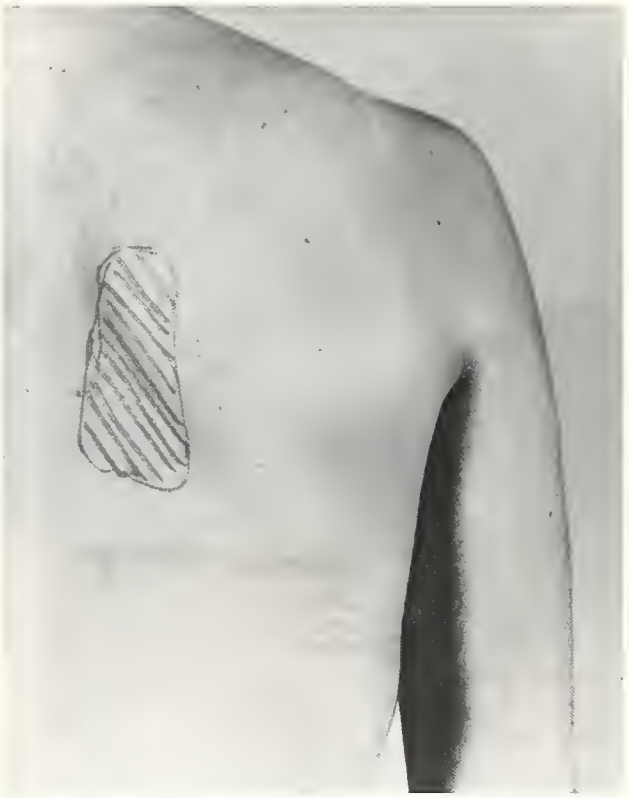


Figure 9. *Notalgia paresthetica. There is medial scapula sensory loss and pruritus.*

Peripheral Neuropathies Predispose to Mononeuropathies

Pressure neuropathies are more common among patients with the diffuse neuropathies: diabetes mellitus, chronic alcoholism, post-inflammatory neuropathy (Guillain-Barre) or metabolic dysfunction (thyroid, uremia, or hepatitis). Examples include peroneal palsy in the aged, CTS in myxedema, or ulnar neuropathy in patients recovering from Guillain-Barre syndrome. Physicians must be aware that patients with peripheral neuropathy are susceptible to secondary peripheral nerve injury.[24]

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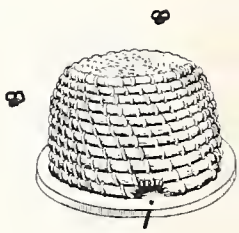
The Management of Bee Hives

Stephen R. Nichols and Francis A. Neelon, M.D.

• *Do patients with exaggerated responses to insect stings need immunotherapy?*

THIS is the *North Carolina Medical Journal,* so we will not drone on about the intricacies of the apiary business, but will instead discuss the current medical management of insect sting reactions. We recently saw a young man in the clinic whose case history clearly illustrates the problems of caring for patients with bee stings.

A healthy 14-year-old boy came to the general medical clinic for evaluation. Twenty-six days ago he had suffered a generalized cutaneous reaction after being stung by a yellow jacket wasp and had come to the Emergency Room. He had been stung on his left ankle and within fifteen minutes his face and extremities were swollen and red; hives had sprung up on his chest, abdomen, and back; he itched a great deal. Thirty minutes later in the Emergency Room, the following observations were made: edema of the left axilla; truncal urticaria; clear lungs; and normal blood pressure and pulse, both of which remained stable. He denied any difficulty breathing or threatened loss of consciousness. He had been stung several times in the past with only a mild, localized response. He had no other allergies nor was there a family history of exaggerated responses to insect stings. He was not treated with epinephrine, but was given an anti-histamine by mouth for his urticaria and an Epi-Pen with instructions to carry it and to use it should he be restung. He was referred to the allergy clinic. In the outpatient clinic, the young man and his mother were concerned about the effectiveness, risks, and necessity of desensitization therapy.



We had only some vague ideas about the management of insect sting reactions on the level of "Refer to allergy clinic." After discussing the case with a couple of immunologists and following up their leads in the library,[1, 2] we found that only forty to fifty deaths a year are attributed to insect stings and that the vast majority (greater than 95%) of these are the result of allergic reactions rather than envenomation itself which requires literally hundreds of stings. It is important to stress that an allergic reaction to an insect sting is not an infrequent occurrence. Approximately 1 in 125-250 people who are stung will have a systemic allergic reaction. Surveys of the general population show that 1 in 25 individuals has had a systemic reaction at some time in the past; 1 in 5 will test as sensitive to at least one of the common insect venoms. What we learned in the library allowed us to appropriately interpret the patient's story and we re-present the case with clarifying comments below.

A healthy 14-year-old

A major point in the natural history and medical management of insect sting reactions is the marked difference between children and adults. More than 90% of insect-sting induced deaths occur in those over 20 years of age. In adults, 90% of systemic reactions are life-threatening, while in those less than 20 years of age only 30% of systemic reactions are so severe. It is presently recommended that all adults who have a systemic reaction to any degree should undergo desensitization therapy, but only those children who have already had a *life-threatening* reaction need such treatment.

boy

Two-thirds to three-fourths of individuals who suffer exaggerated responses to insect stings are male, but this represents increased exposure rather than sex differential susceptibility.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

came to the general medical clinic for evaluation. Twenty-six days ago he had suffered a generalized cutaneous reaction

Insect sting reactions can be categorized into two broad types: localized and generalized (table 1). The local reactions can be either the normal inflammatory response or an exaggeration of the normal response, both of which may have some mild, non-specific systemic symptoms (such as nausea, malaise, or headache) associated with them. The generalized reactions are allergic responses which can be limited to the skin (cutaneous) or can be potentially life-threatening (anaphylactic). Other types of allergic reactions occur, but are very rare.

Table 1: Definition of Insect Sting Reactions

I. Normal Local Reaction: redness and swelling in an area less than 2 inches in diameter with heat and pain that resolves in less than 24 hours.
II. Large Local Reaction: as for a Normal Local Reaction, except a greater area — up to an entire extremity — may be involved or resolution may take longer or both.
III. General Cutaneous Reaction: generalized erythema, angioedema, urticaria, pruritis.
IV. Life-Threatening Reaction: signs of laryngeal edema, bronchospasm, hypotension.

after being stung by a yellow jacket wasp

The insect order *Hymenoptera* contains several members (bees, yellow jackets, hornets, wasps, and fire ants) capable of causing the various reactions noted above. Only yellow jackets and hornets show considerable cross-reactivity and they are often grouped together as vespids, their family name. The prevalence of these insects varies geographically, with wasps and fire ants being more common in the temperate climate of the southern states.

and had come to the emergency room.

Treatment of the reaction is imperative, especially if the reaction is serious, because 2 out of every 3 fatal outcomes from insect stings are associated with a complete lack of medical treatment.

He had been stung on his left ankle and within fifteen minutes

More than 95% of non-fatal reactions occur within the first 30 minutes following the sting. There is evidence that a delay in the onset of reaction beyond 30 minutes is more likely in a fatal reaction.

his face and extremities were swollen and red; hives had sprung up on his chest, abdomen, and back; he itched a great deal.

These are the four basic characteristics of a general cutaneous reaction: angioedema; erythema; urticaria; and pruritus.

Thirty minutes later in the emergency room,

Elapsed time from sting to medical treatment totalled 45 minutes. *Prompt* medical treatment of the reaction is important since the elapsed time from the sting — not the reaction — to medical intervention is less than 60 minutes in 90% of serious but non-fatal reactions, whereas only 5% of fatal reactions are treated within 60 minutes of the sting.

the following observations were made: edema of the left axilla; truncal urticaria;

Once again, the signs of a general cutaneous reaction.

clear lungs; and normal blood pressure and pulse, both of which remained stable.

There is no sign of bronchospasm or pulmonary edema, which are the cause of death in 70% of fatalities, and no indication of hypotension or shock. Combined, these observations indicate that this is not a life-threatening reaction.

He denied any difficulty breathing or threatened loss of consciousness.

These symptoms of cardio-respiratory embarrassment were denied; however, possible laryngeal symptoms (throat fullness or tickle, gagging or difficulty swallowing, or hoarseness or voice change) need to be assessed. Also, chest "tightness" may be the only symptom of bronchospasm.

He had been stung several times in the past with only a mild, localized response.

This is commonly the case and there are no markers, at present, for predicting which individuals will or will not suffer a reaction of increased severity. However, there is good evidence that a change from a mild to more serious reaction does *not* indicate that progression to an even more serious reaction will occur. The rule of thumb is that the severity of the next reaction will be less than or the same as that of the most recent reaction. It is the exceptional case in which the reaction is worse.

He had no other allergies

Atopy is found no more frequently in those who have greater than normal reactions to insect stings than in the general population.

nor was there a family history of exaggerated responses to insect stings.

Such a family history is more common in anyone who has had an exaggerated response to an insect sting, but it is of uncertain significance.

He was not treated with epinephrine,

Epinephrine is the mainstay of treatment for the acute systemic reaction, but may not be necessary in mild systemic (cutaneous) reactions.

but was given an anti-histamine by mouth for his urticaria

Anti-histamines are useful because they lessen the cutaneous response and relieve the pruritis, but they should only be considered after a decision regarding the use of epinephrine has been made and acted upon. The administration of anti-histamines should never delay institution of epinephrine treatment. For the management of all reactions, see table 2.

Table 2: Treatment of Insect Sting Reactions

I. Normal Local Reaction: cold compresses, elevation, non-steroidal anti-inflammatory agents.
II. Large Local Reaction: as for a Normal Local Reaction, plus anti-histamines by mouth.
III. General Cutaneous Reaction: epinephrine, anti-histamines, non-steroidal anti-inflammatory agents.
IV. Life-Threatening Reaction: oxygen and volume expanders — if necessary, epinephrine, anti-histamines, non-steroidal anti-inflammatory agents, aminophylline for prolonged bronchospasm and steroids for other significant, prolonged allergic responses.

and an Epi-Pen with instructions to carry it and to use it

An Epi-Pen is an auto-injector with a hidden needle that delivers 0.3 ml of 1 : 1000 aqueous epinephrine. The Epi-Pen is to be carried when the individual is in settings that provide increased risk of exposure to stinging insects.

should he be restung.

There is a two week period of anergy during which a person will not significantly react to a re-sting. However, 70% of children with systemic reactions are sensitive to more than one venom and could react to a sting by a different insect; on the contrary, 70% of adults are sensitive to only a single venom.

He was referred to the allergy clinic.

This aspect of the case is discussed at the end.

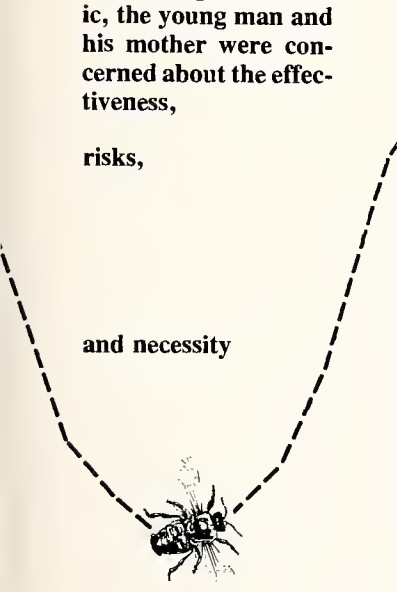
In the outpatient clinic, the young man and his mother were concerned about the effectiveness,

Whole insect extracts were once used in desensitizing vaccines, but are no better than placebo and have been replaced by the use of purified insect venoms. Venom immunotherapy is effective in 97% of cases or more, depending upon what maintenance dose is used.

risks,

Reactions are observed during the induction phase of immunotherapy, but rarely occur once the maintenance dose has been achieved. These reactions are usually not a great problem since they occur in the presence of a physician. Systemic cutaneous reactions that seldom require the use of epinephrine occur in less than 10% of patients, usually early in the induction regimen. Large local reactions occur in 20-25% of patients, usually later in the induction regimen.

and necessity



There is an important difference in the guidelines for managing adults and children by immunotherapy. All adults should have immunotherapy if they have had a systemic reaction and are skin test positive because there is a high likelihood that subsequent reactions will be systemic. In children, re-stinging only rarely produces reactions of increased severity; most show a decrease in symptoms. A prospective study[3] of children who had had large local reactions and no immunotherapy found that 60% of re-stings caused a normal response, 38% a large local reaction again, 1% a general cutaneous reaction, and 1% a life-threatening reaction. A similar study[4] in children with a general cutaneous reaction found that 90% of re-stings resulted in a local reaction; and 10%, a general cutaneous reaction; no life-threatening reactions were observed. This last study was particularly significant because some of the children were being treated with immunotherapy and some were not but no significant differences were found between the two groups in terms of the likelihood or severity of systemic reactions. Based on these studies, only children with life-threatening reactions and positive skin tests need to be treated with immunotherapy.

of desensitization therapy.

Another aspect of immunotherapy regards the duration of maintenance therapy. At present, this cannot be adequately addressed, but preliminary data suggest that it may be possible to discontinue therapy at some point — after several years — because the immune system tends to "forget" its sensitivity to insect venom with time, regardless of ongoing immunotherapy.

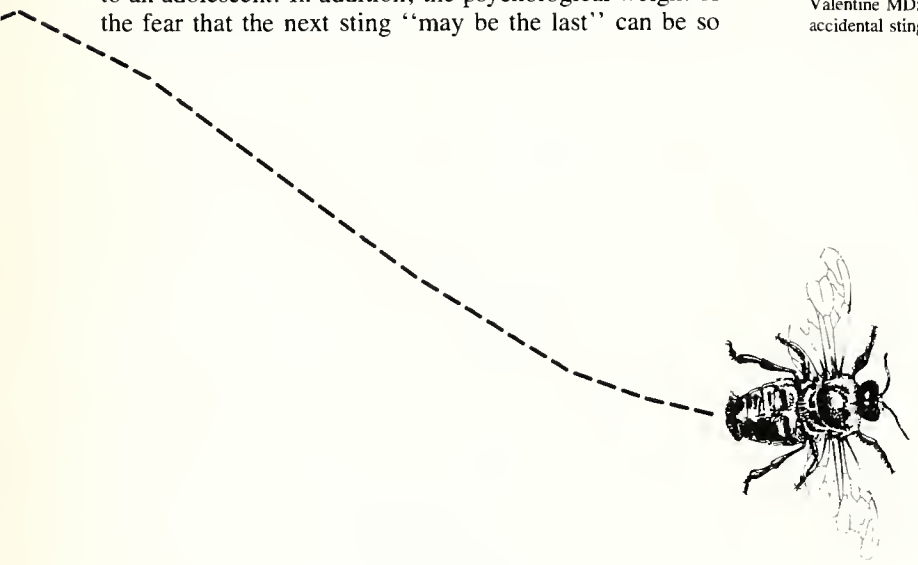
Table 3: Candidates for Immunotherapy

Adults: Everyone with any degree of systemic reaction and positive skin tests.
Children: Only those with a life-threatening reaction and positive skin tests.

The science of medically managing insect sting reactions is thus reviewed. However, there is some art involved in advising individuals who have suffered an insect sting reaction. The most perplexing cases are similar to the one presented: an adolescent with a systemic reaction that does not clearly warrant desensitization therapy. Our example demonstrates the problem of "common sense" precautions to reduce the chance of a re-sting (wearing shoes when outdoors and avoiding activity near trees and bushes or the use of attractants like canned drinks, perfumes, and bright clothing) because they often run contrary to the normal activities of an average adolescent. Recommendations to constantly carry an Epi-Pen are sound, but may not appeal to an adolescent. In addition, the psychological weight of the fear that the next sting "may be the last" can be so great, for the patients or the parents or both, that the patient's activities may become greatly, and unnecessarily, curtailed. These considerations need to be made individually and may require more than a narrow "scientific" perspective in order to achieve optimum medical management.

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SCIENTIFIC ARTICLE

The Patient From Whom I Have Learned the Most: Undiagnosed Pulmonary Emboli Are Still With Us

Herbert A. Saltzman, M.D.

THREE disease processes in the same organ system present a challenge to the doctor. I was confronted with this challenge in January 1970 when a 60-year-old engineer pilot was admitted to my service. He enjoyed excellent health with a background of transient dyspnea during the preceding year and a negative detailed clinical workup including a chest x-ray in March 1969. In December 1969, however, the patient became incapacitated by dyspnea associated with wheezing and a productive cough. A workup elsewhere revealed a paralyzed right hemidiaphragm and bronchitis. Additional studies, including bronchoscopy and gastrointestinal x-rays, were unrevealing. The past medical history was positive for allergies to penicillin and sulfa and for variable rhinitis symptoms.

Significant physical abnormalities at admission to Duke included tachypnea, shallow respirations, use of the accessory neck muscles during respiration, diffuse wheezing over both lungs, tachycardia and trace pedal edema. Admission laboratory findings included leukocytosis with a shift to the left, normal mouth flora in a sputum culture, a paralyzed right hemidiaphragm by chest fluoroscopy, ventilatory obstruction (FEV1 0.9 L — 30%, FVC 1.58 L — 39%, maximal mid-expiratory flow rate 0.41 L/sec — 13%) and a compensated respiratory acidosis with hypoxemia (PaO_2 56 and $PaCO_2$ 46 mmHg, pHa > 7.39).

The initial workup including bronchoscopy, and multiple cytopathologic studies of sputum failed to reveal evidence of malignancy. The hemidiaphragmatic paralysis was presumed to be idiopathic. Vigorous treatment with bronchodilators, physical therapy and broad spectrum antibiotics including tetracycline failed to relieve the profound dyspnea, and the sputum remained infected in character. During the second week of hospitalization a Hemophilus influenza organism, isolated from an endotracheal aspirate, proved resistant to ampicillin and tetracycline but susceptible to Chloramphenicol. A 10-day course was associated with a dramatic diminution of cough, sputum production and wheezing. Despite these favorable changes in the manifestations of bronchitis the patient remained profoundly dyspneic. There were no cardiac, metabolic, hematologic or neuromuscular causes for profound dyspnea, the lungs remained clear of infiltrates and the paralyzed hemidiaphragm could not explain continuing severe dyspnea at rest. For that reason the pulmonary vascular compartment was investigated by means of pulmonary arteriography. (The perfusion scan diagnostic methodologies of that era were not regarded as being diagnostically useful by many pulmonary physicians, including myself, in a setting of variable airway obstruction.) The pulmonary angiogram revealed in both lungs multiple filling defects considered diagnostic of pulmonary emboli. The patient was placed on intravenous heparin therapy. Remarkable improvement ensued with resolution of dyspnea and the residual wheezing. Of related interest was the failure of vascular contrast studies to identify a site of origin for the emboli within the deep veins of the lower extremities and inferior vena cava.

The patient was discharged essentially free of dyspnea or significant other pulmonary symptoms. He took an oral anticoagulant for six months. In ensuing years, right hemidiaphragmatic function substantially returned spontaneously, as judged by fluoroscopic followup. Intermittently he continued to be troubled by rhinitis and asthmatic bronchitis symptoms. These manifestations were treated conventionally.

The solution to this man's clinical illness depended upon recognition that unexplained clinical findings need to be pursued vigorously. The emphasis here is on the clinical findings. This patient had been very vigorous physically without difficulty until the time of the acute illness, except for a transient earlier manifestation of reactive airway disease. At the beginning of his acute illness the finding of hemidiaphragmatic paralysis, wheezing and dyspnea was presumed to reflect the consequences of a bronchogenic carcinoma with obstruction of the airway and invasion of the phrenic nerve by tumor cells. When the diagnosis of bronchogenic malignancy was rejected, on the basis of two independent and complete assessments in different hospitals, the problem of continuing dyspnea and wheezing could still be explained on the basis of superimposed infection in an individual with hyperreactive airways. While initial treatment of a conventional type failed to relieve the clinical manifestations of bronchitis, the identification of a resistant Hemophilus influenza organism in the airway did

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lead to well-directed antibiotic therapy that was clearly effective in controlling wheezing and sputum production. Yet the dyspnea persisted. At this point the clinician had to decide whether this persistent symptom could be explained by the combination of hemidiaphragmatic paralysis and residual obstructive airway disease. Paralysis of the hemidiaphragm, of itself, is not a cause of dyspnea at rest or even with ordinary activity in otherwise healthy individuals and at that point in the clinical course wheezing had essentially cleared. For that reason I did elect to pursue other possible explanations. There were no cardiac, metabolic, hematologic or systemic neuromuscular problems to explain dyspnea. Lung parenchyma was uninvolved by x-ray. Only pulmonary vascular disease remained unexplored as relevant to continuing dyspnea. Happily for the patient, pulmonary angiography identified the occult major cause of dyspnea and subsequent therapy was very successful.

Even in our modern era the diagnosis of acute pulmonary embolism is difficult.[1] In our hospital approximately half of the patients having an acute pulmonary embolism by angiography have VQ scan interpretations other than high probability.[2] Accordingly, those patients with low, indeterminate and intermediate readings, in the absence of a decision to do angiography, may well not be treated for their serious medical problem with a resultant higher morbidity and mortality. In that same population of patients, approximately 15% with high probability scans pursued to angiography failed to demonstrate pulmonary emboli. That group of patients, if not pursued to angiography, may for the most part have received anticoagulant therapy inappropriately with a resultant risk of morbidity and mortality that should not have occurred. These considerations should serve to keep the physician humble about his ability to make consistently accurate diagnoses of the presence or absence of acute pulmonary embolism. Improving diagnostic technologies in the future may help solve the problem.[3-5] A rigorously controlled prospective investigation of how to diagnose acute pulmonary embolism, sponsored by the National Heart, Lung and Blood Institute, will begin this year. The information to be provided by that experiment, we hope, will make diagnostic decision making a simpler task in the future.

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SCIENTIFIC ARTICLE

Spontaneous Pneumomediastinum: A Report of 10 Cases and Review of the Literature

Alan K. Halperin, M.D. and Richard E. Deichmann, M.D.

• *A review of cases, causes and treatment of a rare malady which occurs most often in young people.*

PNEUMOMEDIASTINUM, also termed mediastinal emphysema, can be defined as the presence of free air in the mediastinum. It was first described as a clinical entity by Laennec in 1819 as "interlobular emphysema." Laennec astutely observed that the "affectation is characterized by infiltration of air between lobules of the lung. . . . When extravasation exists near the root of the lungs, it speedily extends to the mediastinum, and from thence crosses to the neck and over the whole subcutaneous and intermuscular cellular substance of the body."[1] It remained a poorly recognized entity until 1939 when Hamman presented seven cases of spontaneous pneumomediastinum characterized by the unique precordial crunching sound which now bears the name "Hamman's sign."[2] Spontaneous pneumomediastinum develops inconspicuously secondary to alveolar rupture in patients with no serious underlying pulmonary disease.[3] It is distinct from traumatic pneumomediastinum in which air gains entry into the mediastinum by means of structures other than the alveolus, i.e., esophageal perforation, tracheobronchial tears, surgical procedures, or mechanical ventilation. Familiarity with pneumomediastinum is important because it must be differentiated from other more serious causes of chest pain and because sometimes there can be serious complications.

The frequency of spontaneous pneumomediastinum is approximately 1 case per 7,000-12,000 hospital admissions.[4, 5] This condition is thought to be more common than previously recognized.[3] Next to pneumothorax, it is the most common cause of chest pain and dyspnea in young patients (15-29 years) admitted to the hospital.[3] Pneumothorax is approximately fifteen times more common than pneumomediastinum.

A recent case of pneumomediastinum stimulated us to review our experience with this unusual entity. Ten cases were identified at either North Carolina Memorial Hospital or the Wake County Medical Center between January 1980 and September 1983.

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Table 1 summarizes the clinical findings in ten patients with spontaneous pneumomediastinum. The incidence was 1 case per 12,344 admissions.

The precipitating factors associated with the development of pneumomediastinum were: cough associated with a respiratory illness and/or asthma (six patients), vomiting (2 patients), minor motor vehicle accident (1 patient), possibly associated with weight lifting (1 patient). The diverse precipitating factors associated with pneumomediastinum are given in table 2.[6-11]

Pathophysiology

Macklin and Macklin reported in 1939 the findings of their classic experiments detailing the pathophysiology of pneumomediastinum.[12] Alveoli are of two types: partitional alveoli, whose bases abut other alveoli, and marginal alveoli, whose bases abut vessels, bronchi, connective tissue, septae, or pleura. Pneumomediastinum occurs when the marginal alveoli surrounding a vessel rupture, thereby allowing air to escape into the connective tissue of the perivascular sheath and then to dissect proximally along the vessel to the mediastinum.[3, 12] From there it may escape into the subcutaneous tissues of the neck, chest, face, abdomen or over the entire body. This escape of air into the subcutaneous tissues is important because it lessens the intramediastinal pressure. If air cannot escape, the pressure in the mediastinum can further increase which can impede blood flow in low pressure veins and cause decreased pulmonary artery flow and venous return. Macklin termed this extravascular "air block."[12] Air can also spread into the interstitial spaces of the lung causing "stiff lungs," distally to the pleura causing pneumothorax if the resulting subpleural bleb ruptures, into the pericardium causing pericardial tamponade, and into the abdomen causing pneumoperitoneum or pneumoretroperitoneum.

The alveolus will rupture whenever pressure within the perivascular sheath is negative relative to the intra-alveolar pressure. Partitional alveoli are spared from rupture since increased intra-alveolar pressure can be dissipated among neighboring alveoli via the pores of Kohn. Pneumomediastinum occurs in the presence of atelectasis since the neigh-

Table 1
Clinical Findings in Patients with Spontaneous Pneumomediastinum

Case	Age (yrs)	Sex	Precipitating Factor	Dyspnea	Chest Pain	Hamman's Sign	Subcutaneous Emphysema (palpable)	Complications
1	18	M	?Weight Lifting ?Spontaneous	+	+	+	–	–
2	17	M	Asthma	+	–	+	+	Small Pneumothorax
3	11	F	Gastroenteritis and Vomiting	–	+	+	–	–
4	15	M	Gastroenteritis and Vomiting	–	–	+	+	–
5	15	M	Asthma	+	–	–	–	–
6	56	M	Motor Vehicle Accident	–	+	–	–	–
7	21	M	Upper Respiratory Illness and Cough	+	+	+	+	–
8	9	F	Upper Respiratory Illness and Cough	+	–	–	+	–
9	2	M	Pneumonia	–	–	–	–	–
10	48	F	Chronic Obstructive Pulmonary Disease	+	+	–	+	–

boring alveoli undergo compensatory over-inflation, thus producing the conditions favoring rupture. Pneumomediastinum also appears when intra-alveolar pressure is greater than that of atmospheric pressure. Pulmonary disease increases the risk of alveolar rupture.[4]

Review of Clinical Findings

The most common chief complaints in our patients were chest pain (5/10 patients) and dyspnea (6/10 patients). The chest pain was located substernally and occasionally radiated to the back or neck. It was frequently aggravated by coughing, swallowing, deep inspiration, and the supine position and was partially relieved by leaning forward. Dyspnea, when present, was usually mild and often related to other precipitating factors such as asthma, upper respiratory illness, etc.

The most common physical findings were Hamman's sign (5/10 patients) and subcutaneous emphysema (5/10 patients). Hamman's sign is a precordial crunching sound and is best heard when the patient is in the left lateral decubitus position.[2, 4] It is synchronous with the heart beat and accentuated by expiration. It is sometimes confused with the friction rub associated with pericarditis. Hamman's sign, though helpful, is not pathognomonic for pneumomediastinum and has been noted in bullous emphysema, pneumothorax, and dilation of the lower esophagus.[4] Subcutaneous emphysema appeared over the extrathoracic trachea and on one or both sides of the neck in five patients. In one patient it extended over the left eyelid, face, neck, and abdomen (Patient 10). One patient in our series suffered a small right pneumothorax which resolved spontaneously without placement of a chest tube.

X-ray Findings

The definitive diagnosis of pneumomediastinum is made by radiologic evidence of free air in the mediastinum. On the posteroanterior chest film, radiolucent streaks of air in the mediastinum, which surround the pericardium, reveal the thin dense line of the anterior mediastinal pleura. The lateral film demonstrates retrosternal free air and clear definition of mediastinal structures such as the aorta. Subcutaneous emphysema in the neck was present on the chest x-ray in all of our patients at the time of presentation.

Differential Diagnoses

Pneumomediastinum must be differentiated from other

Table 2
Causes of Pneumomediastinum

I. Rapid inflations and deflations of the lungs plus increased intra-alveolar pressure.
  Cough
    acute infections
    chronic lung diseases (asthma, sarcoidosis, neoplasm)
  Atelectasis
    pneumomediastinum of newborns
    infections
    foreign body aspiration
  Miscellaneous
    motorcycle riding
    complications of mechanical ventilation
II. Decreased caliber of pulmonary vessel
  Pulmonary embolus
III. Combination of I and II
  Valsalva's maneuver (childbirth, blowing a wind instrument, marijuana, smokers during breath holding)
  Athletes (weight lifting, mountain climbers, heavy breathing after exercise)
  Vomiting (gastroenteritis, diabetic ketoacidosis)
  Submarine escape training, deep sea diving, bomb blast
IV. Trauma
  Perforation of esophagus or tracheobronchial tree
  Chest wounds
  Surgical, dental, or diagnostic procedures

causes of chest pain. Common problems which need to be excluded are: cardiac causes (ischemic heart disease, pericarditis), other pulmonary causes (pulmonary embolus, pneumothorax, pneumonia), musculoskeletal causes (costochondritis, degenerative joint disease) and esophageal causes (spasm, reflux esophagitis, rupture). In two of our patients, chest pain came on after vomiting. In this situation esophageal rupture must be considered. In esophageal rupture the pain is more severe and there is a rapid progression of dyspnea, fever, and signs of vascular collapse. The chest x-ray may show pneumomediastinum, widening of the mediastinum, and frequently pneumothorax and pleural effusion. The diagnosis can be confirmed with an esophagogram. Other causes of chest pain can usually be distinguished by the history, physical examination, chest x-ray, electrocardiogram, and occasionally other laboratory tests. It is important to distinguish air in the pericardial space from air in the mediastinum. In pneumopericardium, the air does not rise above the upper limit of the pericardium on the PA chest x-ray with the patient in the erect position. If decubitus x-rays are taken, pericardial air will shift within the pericardial sac, whereas mediastinal air will not move.[6, 7]

Course and Complications

Pneumomediastinum is usually a benign condition which is rare in adults and more common in neonates.[3, 13] The chest pain is improved within one day and there is resolution of the air on the chest x-ray within 3-5 days. If the free air in the mediastinum accumulates and does not escape into the soft tissues, the pressure in the mediastinum increases. Dissection into the pericardial space can cause tamponade which requires pericardiocentesis.[15] Air can also dissect into the interstitial spaces of the lung causing "stiff lungs" or distally to the pleura where a bleb can form. Pneumothorax results if the bleb ruptures. Unlike pneumothorax, pneumomediastinum usually does not recur.[14]

Treatment

All patients with pneumomediastinum should be thoroughly evaluated by a history, physical exam, and chest x-ray. Particular emphasis should be placed on the recognition of serious complications. Four hours of 95% oxygen decreases the partial pressure of nitrogen in the blood which promotes the diffusion of nitrogen from the interstitium into the blood.[16] This increases the rate of resorption of the mediastinal air. Patients should be given appropriate analgesia and treatment of the underlying disorder predisposing to pneumomediastinum. If complications arise, they should be aggressively treated.

Acknowledgment

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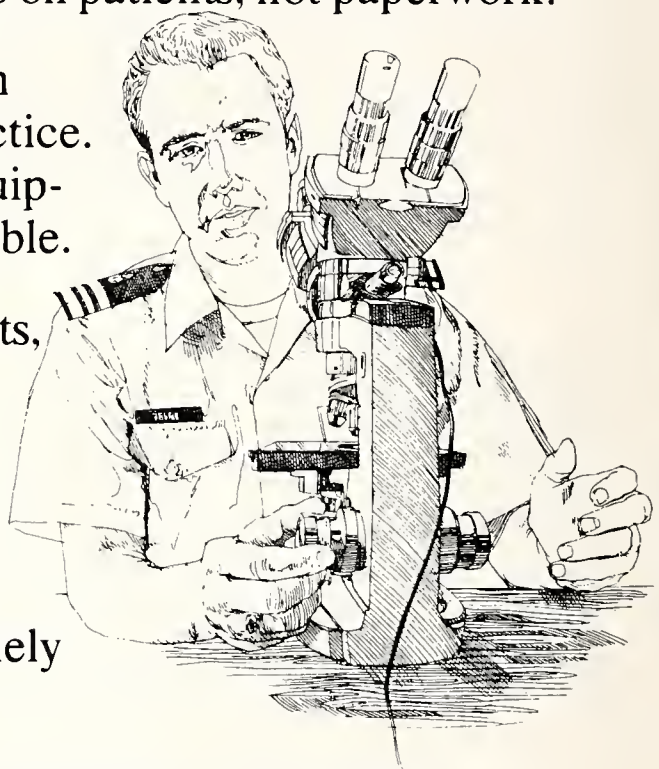
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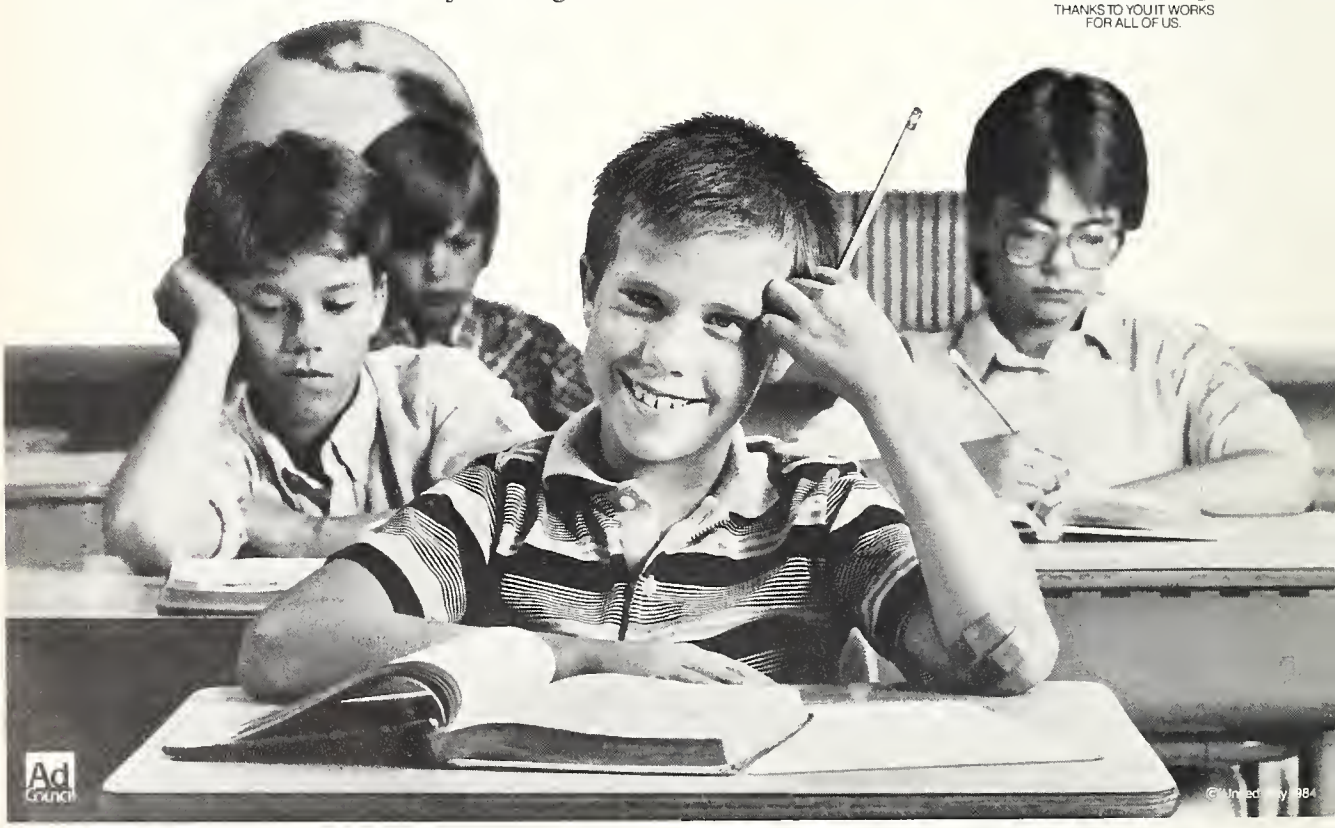
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SCIENTIFIC ARTICLE

Interactions Between Digitalis and Antiarrhythmic Drugs

Thomas L. Wenger, M.D. and Harold C. Strauss, M.D., C.M.

• *A review of recent studies of the interactions between digitalis and several antiarrhythmic drugs.*

IN the last several years previously unrecognized actions between digitalis and certain antiarrhythmic drugs have come to light. These interactions can be viewed as having either a pharmacodynamic mechanism or a pharmacokinetic mechanism.

Pharmacodynamic interactions are those in which the response to various drugs is enhanced or diminished by the response to another. Interactions between digitalis and antiarrhythmic drugs include the decrease in automaticity and conduction in the sinus and AV nodes that occurs in combination with beta adrenergic blocking drugs or slow inward current blocking drugs. By separate mechanisms of action, each of these drug types is capable of reducing sinus node automaticity as well as sinus node and AV node conduction so that, when used together, they tend to augment one another's effects. Another well known pharmacodynamic interaction of digitalis with antiarrhythmic drugs involves the use of digitalis in patients with atrial fibrillation to overcome the anticholinergic effects of drugs such as quinidine and disopyramide on ventricular response rate.

Pharmacokinetic interactions are those in which one drug affects how another is absorbed, distributed or eliminated. The interactions of digitalis with certain antiarrhythmic drugs are complex in nature and serve as the focus of this review article. Table 1 gives a list of antiarrhythmic drugs that have been suggested to cause an increase in serum digoxin concentration when both are administered concurrently. Drugs are ranked in decreasing order of their ability to raise the serum digoxin concentration. To understand the potential clinical significance of these interactions, it is important to understand the mechanisms by which they occur.

The first reports of a pharmacokinetic interaction between digitalis and antiarrhythmic drugs focused on the rise in serum digoxin concentration that occurs when it is coadministered with quinidine. This interaction was first described independently by Ejvinsson,[1] Leahey et al, [2] and Doering and Glumel[3] in 1978. Since these initial observations, continuing research has elucidated many questions about this interaction but several important questions still remain unanswered.

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The prevalance of the digoxin quinidine interaction appears to be in excess of 90% of patients who are exposed.[4, 5] The magnitude of the increase in serum digoxin concentration has been reported to be quite variable from patient to patient, most studies reporting that at therapeutic concentrations of quinidine a 100 to mean 125% increase in serum digoxin concentration occurs (table 2). While the magnitude of the increase appears to be independent of the serum digoxin concentration, it is clearly dependent on serum quinidine concentration.

When quinidine is given as a loading dose to a patient who is on a steady state digoxin regimen, the serum digoxin concentration rises rapidly. Continued administration of quinidine results in a continued slow increase in digoxin concentration, ultimately reaching a plateau after about 7-14 days. This initial increase is most consistent with an alteration in tissue distribution of digoxin, while the more gradual later rise is consistent with a mechanism that involves a reduction in digoxin's elimination rate.

Any change in tissue binding of a drug causes a change in the apparent volume of distribution. This is defined as the volume that would be occupied by the total amount of the drug in the body if it were uniformly distributed at the concentration found in serum. Thus, the apparent volume of distribution equals the amount of drug in the body divided by the serum concentration. If the amount of drug in the body remains constant, an increased serum digoxin concentration must therefore reflect a decrease in the volume of distribution. This mechanism is considered to be the explanation for the early rise in serum digoxin concentration. A loading dose of quinidine usually results in a 30 to 40% decrease in the apparent volume of distribution. Leahey et al[6] have suggested that there is little effect on the

Table 1
Antiarrhythmic Drugs That Cause Pharmacokinetic Interactions with Digitalis

—Quinidine
—Verapamil
—Amiodarone
—Nifedipine
—Flecainide
—Propafenone

digoxin volume of distribution when the serum quinidine concentration falls below 1.9 μg/ml.

Elimination of digoxin is dependent on glomerular filtration and renal tubular reabsorption and secretion. In addition, hepatic clearance of digoxin may be important, accounting for as much as 12% of total body clearance. In patients with declining renal function, the reduced renal clearance of digoxin increases the significance of hepatic elimination. It is important to consider all three routes of elimination in evaluating the digoxin quinidine interaction. Available data suggest that quinidine reduces renal clearance by blocking tubular secretion. The range in reduction of renal digoxin clearance is wide but appears to average 30 to 40%. This results primarily from a change in tubular secretion, since creatinine clearance remains unchanged.[7] The influence of quinidine on renal clearance of digoxin can be estimated by subtracting renal clearance from total body clearance or can be approximated by evaluating total digoxin clearance in patients who are functionally anephric.[8, 9] The decrease in non-renal clearance also appears to average between 35 and 45%. This decrease appears to be independent of the serum quinidine concentration.

In summary then, the increase in serum digoxin concentration after quinidine co-administration results from a decrease in digoxin tissue binding, which leads to a decrease in its volume of distribution and a decrease in renal and non-renal elimination.

The tissue compartment from which digoxin is displaced may play a critical role in determining whether the rise in serum digoxin concentration will be associated with an increase in digoxin effect and toxicity. For example, if the displacement occurs only from non-specific binding sites in the body, then an increase in serum digoxin concentration will likely cause an increase in the action of digoxin. If, on the other hand, displacement occurs at the receptor site responsible for its actions, such as sodium, potassium (Na^+, K^+) ATPase, then the increase in serum digoxin concentration may not be accompanied by an increase in effect or toxicity and, in fact, could be associated with a decrease in digoxin action. This important area of basic research remains unsettled and is critical to an understanding of the expected clinical effects of the interaction.

An effort to elucidate the clinical significance of the digoxin-quinidine interaction has centered on efforts to demonstrate the clinical effects of the increase in serum digoxin concentration. Indices that have been used to evaluate the effect of a rise in serum digoxin concentration on function are assessments of the PR interval as a reflection of vagomimetic effects and of systolic time intervals reflecting the direct effects of glycosides on contractility. Such studies are complicated since both quinidine and digoxin are capable of having multiple effects on electrocardiographic and systolic time intervals. Leahey et al[10] examined the change in serum digoxin concentration during administration of four antiarrhythmic agents: quinidine, procainamide, disopyramide and mexiletine. Only quinidine caused a significant increase in serum digoxin concentration (figure 1). When the effects of these four agents on the PR interval were examined, only quinidine caused an increase in the PR interval even though each of these antiarrhythmic drugs tends to have a similar effect on the AV node (figure 2). One might surmise, therefore, that the increase in PR interval was secondary to the rise in serum digoxin concentration rather than the co-administration of quinidine.

The effect of co-administration of quinidine on contractility has been assessed by systolic time intervals.[11] Though the data support the view that the increase in serum digoxin concentration results in an increase in cardiac effect, the study does not really address how large is the increase in cardiac effect resulting from the increase in serum digoxin concentration.

Ultimately, the significance of this interaction needs to be defined by clinical observation as well as by basic and clinical research. Several case reports have cited experience in which digoxin toxicity developed following quinidine administration despite a constant digoxin dose, stable renal function and a normal potassium level. On the other hand, Walker et al, reporting on the observations of the Boston Collaborative Drug Surveillance Program, noted a rate of 1.1 reactions per 100 patient days in 4,027 patients who received digoxin alone, 1.1 reactions per 100 patient days in 249 patients who received quinidine alone, 2.9 reactions per 100 patient days of observations in 142 patients who received digoxin and quinidine. The difference in reaction rates in patients receiving both drugs and the sum of the rates in patients receiving the drugs separately were not significantly different.

Any analysis of the clinical impact of co-administration

Table 2
Effect of Quinidine on Serum Digoxin Concentration

		Serum Digoxin Concentration			
		Quinidine		Digoxin +	
	n	Concentration	Digoxin	Quinidine	% change
Leahey et al 1978	27		1.4±0.7	3.1±1.4μg/ml	121
Ejvinsson 1978		2.1μg/ml	0.85	1.6μg/ml	88
Doering 1979	38	2.32μg/ml	0.98±0.37	2.47±0.64μg/ml	152
Mungall et al 1980	15	2.82μg/ml	0.72±0.28	1.41±0.43μg/ml	96
Leahey et al 1980	22	2.7μg/ml	1.2±0.8	2.4nmol/1	100

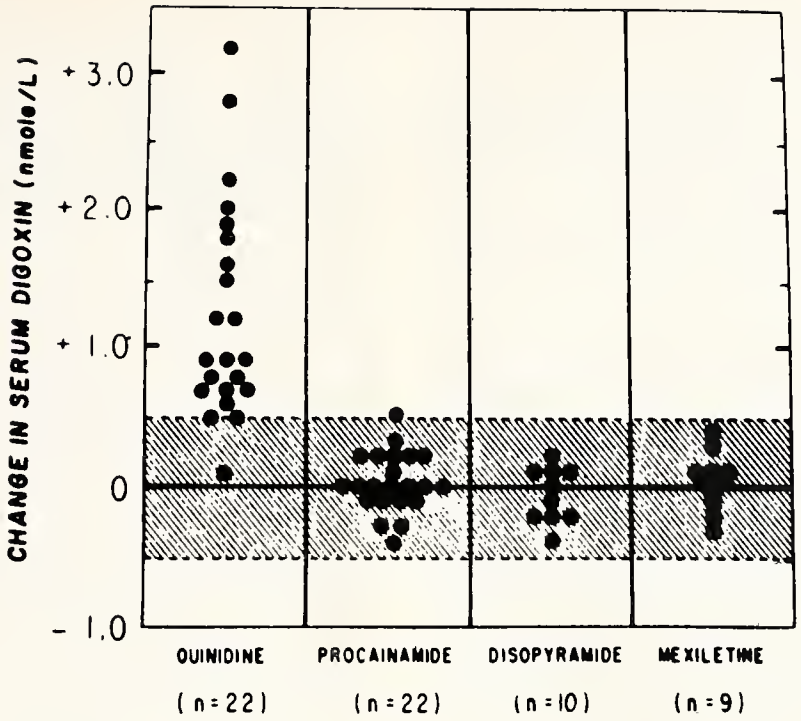


Figure 1. *Each point represents the difference between serum digoxin concentration before and after administration of the antiarrhythmic drug.*

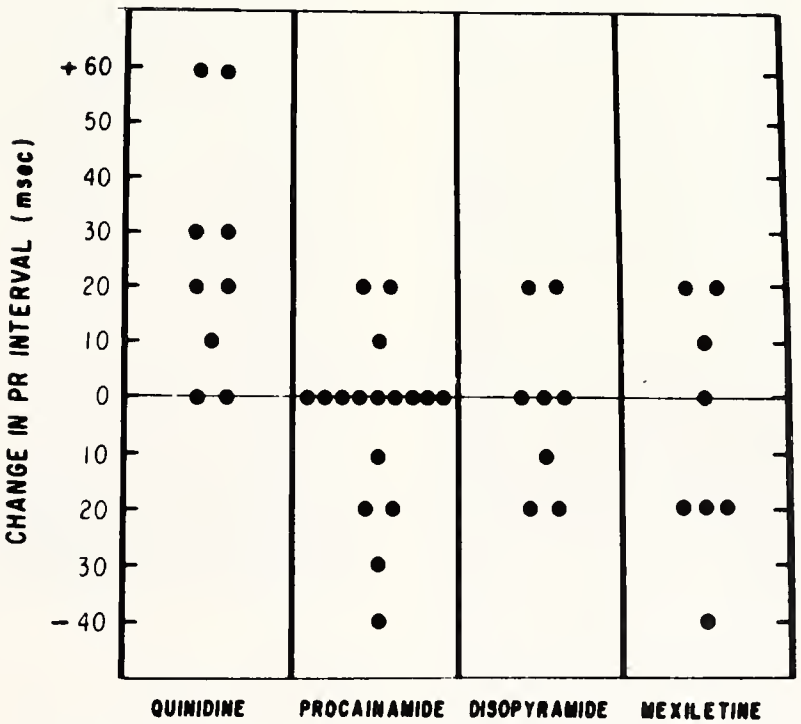


Figure 2. *Each point represents the difference in PR interval before and after administration of the antiarrhythmic drug.*

of digoxin and quinidine on digoxin toxicity will depend on the serum digoxin concentration prior to quinidine exposure, the serum quinidine concentration and the toxic threshold for digoxin in that particular patient or patient population. Clearly, patients whose serum digoxin concentration is at the upper level of the therapeutic spectrum will likely have a higher prevalence of toxicity than those with serum digoxin level concentrations at the lower level of the therapeutic spectrum. Such confounding variables make definitive conclusions from the clinical data difficult to achieve.

Although this paper has concentrated on the digoxin quinidine interaction, data also exist on a digitoxin quinidine interaction. Although initial reports suggested that such an interaction did not exist, Fenster et al[13] showed that the interaction appeared to reach the same magnitude as the digoxin quinidine interaction if assessments were made far enough out in time. The different time course relates to the much longer half-life of digitoxin. Although there appears to be little change in the apparent volume of distribution of digitoxin, elimination is prolonged. Because of the prolonged elimination half-life of digitoxin, the time taken to reach a new steady state may be in excess of one month. It is thus unclear whether digitoxin can be considered an alternative to digoxin when considering quinidine therapy in a patient requiring a digitalis glycoside.

Besides quinidine, other antiarrhythmic drugs have been shown to have effects on digoxin kinetics. Data by different investigators suggest that verapamil causes a 60 to 75% increase in serum digoxin concentration via reduction in both renal and non-renal clearance and perhaps also by reduction in the volume of distribution of digoxin. Pedersen et al[14] found that this digoxin verapamil interaction was dose dependent and partially reversible with continued therapy.

Amiodarone, an experimental antiarrhythmic drug, appears to produce a significant increase in serum digoxin concentration if the amiodarone is given in large enough doses. A recent study indicates that an increase in serum digoxin concentration may be particularly marked in children, ranging between a 69 and 278% increase in the serum digoxin concentration in a prospective study and up to 800% in a retrospective study.[15] The authors of this investigation suggested that the interaction might be more significant in children because of a greater rate of renal tubular excretion of digoxin in children.

Initial reports suggesting a 45% increase in serum digoxin concentration during co-administration of nifedipine and digoxin have not been confirmed in subsequent studies. Small and as yet unsubstantiated claims for an increase in serum digoxin concentration have also been reported for flecainide and propafenone. The existence of such interactions, the magnitude of the effect and the clinical significance remain to be elucidated.

What practical suggestions can be offered to the clinician caring for a patient who requires digitalis therapy and antiarrhythmic drug therapy? The first practical suggestion is obviously to reassess the need for digitalis or for the antiarrhythmic drug. If both forms of therapy are considered essential it is probably still prudent to follow the guidelines elucidated by Dr. Bigger in 1981.[16] He suggested that the dose of digoxin be decreased when quinidine is added. If a loading dose of quinidine is given, then the digoxin dose for that day can be omitted and, if quinidine is continued, the digoxin maintenance dose should be decreased by about one half. It may be useful to follow serum digoxin concentrations since the magnitude of the interaction can be variable. In any case, careful clinical evaluation of the patient for a period of time equivalent to at least five times the elimination half-life of digoxin after addition of the quinidine is essential. An alternative approach is to replace quinidine with another antiarrhythmic drug, such as procainamide or disopyramide, that does not affect the serum digoxin concentration. Guidelines for coadministration of digitalis and verapamil and amiodarone are even less clear. Although it would be prudent to follow the serum digoxin concentration as a guide to readjusting the digoxin dose, clinical evaluation of the patient remains of paramount importance.

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SPECIAL ARTICLE

Thoughts on the Beliefs of Religious and Medical Institutions

Albert D. Warshauer, M.D.

• *One physician's look at some of the most difficult issues facing the world near the end of the twentieth century.*

Introduction

We begin with definitions.

"Education" is the acquisition of a system of beliefs and skills.

An "institution" is a group of different people, who by being partially restrained to one another, acquire one or more significant new properties not found by testing the individual people. Thus, to prove that an institution exists, we must show first, a partial restraint between different people, and second, a significant new property.

An institution which itself largely controls the entry and exit of its members is "self-perpetuating."

Is medicine a self-perpetuating institution? Yes. People must pass tests to be allowed to practice medicine; and their work, at least in hospitals, is subject to staff review. New properties are that physicians can prevent or ameliorate many diseases better than can lay people. Physicians largely control the education and tests of people who wish to become and remain physicians. By their common education, physicians acquire a system of beliefs.

Religions likewise often are educating, self-perpetuating institutions. The partial restraint is the religion's criteria for membership. New properties include a special system of beliefs and social meetings of the members of the group. (A person could have a unique system of beliefs and live as a hermit, but such people are few compared to the members of organized religions.)

Can the membership of medical and religious institutions overlap? Yes, of course. Some physicians belong to religions; others do not. Some members of religions are physicians, whereas others are not.

The beliefs of an institution can be a source of problems. Sometimes the beliefs of one institution are contrary to the interests of another institution or opposed to the welfare of the whole society. Sometimes the beliefs contradict one or more natural laws, or the beliefs have an unusual historical origin. Beliefs considered to be true without regard to tests are said to be "Sacred."

"Bias" is a certainty of belief without supporting tests or evidence. "Prejudice" is bias favoring one's own advantage and to the disadvantage of someone else. Bias which operates to one's own disadvantage is "reverse prejudice."

From the viewpoint of a scientist who does not belong to a religious or medical institution, Sacred beliefs tend to bias the person who holds them. But a member of the religious or medical institution which holds Sacred beliefs often considers these beliefs to be irrefutably true, and therefore to be neither bias nor in need of testing.

Underlying Theorems

Several scientific theorems apply to religious and medical institutions and to their interactions.

1. People and institutions sometimes want more rights (freedoms) and less duties (responsibilities).

Explanation: Freedoms often can aid our satisfaction of needs and desires, while duties can inhibit our efforts. In other words, more freedoms and fewer duties sometimes promote survival and growth.

2. Institutions and societies often seek stability.

Explanation: Some stability is necessary for the formation, maintenance, and growth of institutions and societies.

3. Need for feedback from actions.

For social stability, the people in control must be accountable to the people who are affected by their decisions. Rights and responsibility must coincide to a reasonable degree. Otherwise, instability and social conflict sooner or later become inevitable.

4. Limited rights.

Rights are not total. Our freedoms extend only to where they infringe on the rights of others. This limitation applies to freedoms of speech, press, and systems of beliefs.

5. On existence of bias.

Sometimes, the resolution of a problem affects the welfare of the participants. That is, the people and their institutions may gain or lose privileges and money by what actions are taken.

Whenever an institution has a self-interest in how a problem is resolved, we can suspect the existence of bias by the institution and its members. Religious and medical institutions share this propensity to be biased.

6. On visibility of bias.

Ordinarily, neither people nor their institutions are aware of their own bias.

A person's own bias may be obvious to outsiders, but it is transparent to himself. It has been said that prejudice is the

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only thing which cannot recognize itself in a mirror.[1] (Personally, I have almost no bias or prejudice, and cannot understand why people laugh when I say this!) Usually more heat than light is generated by accusing someone of bias.

7. On the difficulty of changing bias.

Bias is not hardened steel — but occasionally it does seem to be cast in concrete.

Bias sometimes can be changed by presenting facts which contradict the bias, and by asking the person to explain how the facts can mesh with his bias.

Or, if the subject holds inconsistent beliefs, you can ask how this happened. Did he acquire one of the inconsistent beliefs first, or both together? Did he first learn (a) that all members of religion X were Communists, or (b) that all of them were rich Capitalists?

We should not be very optimistic regarding changing a person's bias. If a person could easily realize that he was biased, he probably would not have become biased in the first place.

Therefore, in resolving problems between different institutions or between an institution and the whole society, we usually should seek social stability and limit the infringement of rights, and only secondarily try to influence the belief systems of the protagonists.

Origin of Problems Due to Different Beliefs

The belief system of one institution may or may not agree with that of a second institution or with the whole society. When the parties agree, their interactions will likely be easy and without problems. Religious and medical institutions often are supportive and helpful to each other.

However, when the institutions have competing beliefs on a subject of mutual interest, friction becomes likely. If one or both institutions regard their beliefs as "Sacred," resolution of the problem becomes difficult.

Illustrations

Let us examine actual cases and possible resolutions.

1. Suppose the religion refuses medical care

A member of a religious sect may refuse medical care for himself or for dependent members of his family. Since the member is responsible, he should be permitted control. The physician has no inherent right to object unless the physician is willing to assume responsibility for the outcome.[2]

Suppose the physician objects to not operating on a newborn baby who has spina bifida and lower extremity paralysis.

If the medical institution and society require the operation over the parent's objections, they should offer to raise the baby. Otherwise, they seek rights without responsibility. Physicians who insist on operating on such patients, fully knowing that they are imposing an unwanted, serious burden on the family, are irresponsible.

What about the baby's rights? Since a baby cannot voice his opinions, someone must speak for him. It would seem that the parents, who gave birth to the baby and are responsible for his prolonged care, have more right to represent the baby than the physician who only recently became involved and is not responsible for the later daily care of the baby.

It is arrogance on the part of the physician to assume that his superior knowledge gives him a right to impose unwanted burdens on families. Here, the physician's job is to advise, not to decide. If the physician truly has superior knowledge, let him employ it for persuasion, and not for coercion of the responsible parties.[3]

2. On birth-control, sterilization, and abortion

Suppose an institution, such as a religion, wants to outlaw contraception, sterilization, and abortions. Then the members of this institution should assume responsibility for the resulting offspring. If they personally avoid this responsibility, their intentions become suspect.

If a pregnant patient wants an abortion, she is within her right, since she and no one else is responsible for the baby continuing to live.

If people want the right to prevent this abortion, then they should accept responsibility — which could mean raising and feeding the child. Otherwise, their actions are a cheap effort to obtain a right without a corresponding duty.

3. On suicide and euthanasia

Suppose a patient, who is terminally ill with cancer or another incurable illness, wants to commit suicide. Society has no forcible right to prevent this suicide since it has no way to improve the patient's lot.

If the ending of life requires an initiative, such as injection of a drug, the physician is fully within his rights to refuse. However, if the termination simply requires that extraordinary measures such as ventilators and dialysis machines be discontinued, we should accede to the patient and family's request.[4]

To actively kill is one thing; to actively prolong misery is quite a different matter.

4. Blood transfusion

A religious sect allows its members to receive only their own blood. For elective procedures, many surgeons collect blood from these patients preoperatively. If blood is needed, the patient's own blood is used.

However, suppose a patient in need of major surgery has religious beliefs which prohibit his receiving a blood transfusion from other donors and the patient cannot supply his own blood units.

The physician has a choice. He can either treat the patient and respect his religious beliefs, or he can refuse to care for the patient. But the physician should clarify to the patient exactly what he thinks are the options as well as the contingencies in the event of a mishap.

For example, an anesthetist might say, "I will do everything possible to avoid giving you a blood transfusion. However, if something unexpected happens which places you in critical danger, I will administer a transfusion. It is against my religious beliefs to allow patients to die during an operation from not receiving a needed transfusion. I respect your religious beliefs, and hope that you also can understand mine."

If the patient wants me to promise not to transfuse him, I might say, "I will gladly do so, providing you will promise that you will not be in urgent need of a transfusion."

The problem is resolved by realizing that one person's rights stop where they start infringing upon another person's rights. Religious beliefs should not be an excuse for

what, under other circumstances, would be clear and obvious malpractice.

5. Autopsy

Suppose a religious group wants to prevent autopsies. If the cadavers during life were their relatives, the religious group has legal control. Otherwise, if not related, the religious group wants to interfere with medical education without accepting responsibility.

6. Special diets

Suppose patients want, or contrarily do not want, some special foods. Such diets usually are a minor inconvenience, and can be catered without serious problems.

7. Allergy as a cause of bronchial asthma

It is not only patients who are affected by bias. Physicians also have been taught religious and medical beliefs.

A basic tenet of allergy is that different species of animals respond notably differently to antigen-antibody reactions.

Physicians who in their youth were biased in favor of the separate creation of species will tend to favor this tenet. They want the animal species to be different, and will tend to avoid critical tests of this hypothesis.

Contrarily, physicians who favor evolution will be suspicious of this tenet.

For example, bronchial asthma in children is sometimes attributed to allergy to food, such as cow's milk. No experimental animal has been found to develop bronchial asthma from drinking cow's milk. Cats drink milk, but have you ever seen a cat which routinely developed asthma after drinking milk? I have not. Nevertheless, this hypothesis of allergy was thought to be a reasonable etiology of bronchial asthma in children.

8. The right of physicians to decide on medical care

Because of our superior medical knowledge, we often assume that we have a right to decide on the care of patients. In fact, our decisions usually do benefit everyone concerned. However, whenever a right is divorced from responsibility, a prospect exists for abuse.

Part of the current belief system of physicians seems to be that life should be prolonged or saved. Ordinarily, this belief is an excellent goal. However, sometimes the quality of the extended life seems to be less important than its prolongation.

Suppose a patient has a severe chronic brain syndrome and is vegetating in a nursing home. No visitors come to see the patient. A leg becomes gangrenous. The surgeon decides that an amputation should be done, and I anesthetize the patient. The surgeon and I receive a fee, but society pays the bill. The patient vegetates a few months longer and dies.

Society at large, not the surgeon and myself, has been taken advantage of because physicians have received a right without a corresponding responsibility.

A common way of running up a large medical bill is to place a patient on a ventilator and intravenous feeding during the final few hours or days of a terminal illness. These large bills may help keep hospitals financially solvent; but, for the entire society, this kind of medical care is a waste of resources.

9. On medical fees and malpractice awards

Physicians like to receive high medical fees and not to be subject to high malpractice awards. The general public favors the opposite, low medical fees and high malpractice awards. The malpractice lawyers who work on a contingency basis, of course, want no cap on malpractice awards.

Both the physicians and the public apparently want maximal rights without matching responsibility. Neither side will admit that fees and malpractice awards are linked problems. As a result, the public fears medical fees and physicians fear malpractice suits.

It seems doubtful that this problem will be resolved until this link between medical fees and malpractice awards is acknowledged by both sides.

10. Indifference to large social needs

The belief system of physicians often emphasizes individual patients. Taking care of individual patients brings substantial financial rewards. But little monetary gain accrues to physicians from attending to large social needs.

Let us examine the record. We occasionally have done very well in answering social needs. Physicians in cooperation with other organizations accomplished widespread polio immunizations. Poliomyelitis has become a rare disease in the United States.

But in a few areas, our record is dismal.

- Many physicians were passive during the Vietnam war. Few took a public stand, one way or the other.
- Physicians also were largely inactive during the civil rights struggles a few decades back.
- Nor, as a group, did we distinguish ourselves in promoting the use of seat-belts and in opposing drunk driving.

However, we do wake up promptly when our economic interests are affected. When dentists apply for operating privileges in hospitals, we become alert.

When laymen regard the American Medical Association as a union, they have more than trivial grounds for their opinion. Physician organizations have been politically active in aiding candidates who favor our economic interests. But what have we done in favoring candidates who will take a stand on controlling overpopulation and slowing or stopping the nuclear arms race? Not much.

Human overpopulation and the nuclear arms race are two underlying problems in the world.[5, 6] Related problems include religious bigotry, terrorism, our lack of a reliable means for settling international disputes without wars, and the loss of valuable plant and animal species. In the United States alone, our present rate of depletion of natural resources should be alarming to a thoughtful observer.[7]

Physicians put in an artificial heart and keep one patient alive a few extra weeks. At the same time, we ignore that more than 10,000 children are being born who are fated to starve before they are six years old. I find nothing wrong with heart research, and strongly support it. However, I wonder about our system of medical beliefs which so largely ignores the overpopulation in the United States and the rest of the world.

11. On international cooperation and conflict

The indifference of physicians concerning international issues is striking. It is a rare event when a physician writes a letter to the editor or publicly takes a stand against terrorism.

In World War II, more than a million children of religion

X were murdered. Some children were bled to death by the Nazis to provide blood for transfusions of soldiers. Some Nazi physicians killed people by experiments involving hypoxia and by submersion in ice water. Was there a public outrage by physicians? I saw little concern, a few letters and articles regretting this unpleasant chapter of history. The Holocaust did not upset many physicians of religions Y and Z, perhaps because the victims belonged to a different religion X. So far as I can see, physicians have about the same religious bias as the remainder of the population.

12. On the future of medical practice

Our current medical belief system holds that medical care is best provided by physicians and medical institutions engaged in private practice. This method of medical care furnishes strong incentives to physicians and rewards those who are skillful and work hard.

In a wealthy society, the private practice of medicine can flourish. Medicine has made tremendous advances in the United States.

However, as the United States becomes progressively more overpopulated, our average wealth shrinks. In a poor society, the private practice of medicine can become a destabilizing influence. If the leaders of society find that the private practice of medicine is no longer affordable, it can be replaced by some other kind of medical practice.

I have heard a few young physicians say: "Socialized medicine is inevitable. So we should make some money while we can." With this attitude, accompanied by an indifference to the major problems facing our people, such predictions could well come to pass.

At present, the problem of human overpopulation seems to be getting worse. The related problems of the nuclear arms race, religious bigotry, and terrorism do not seem to be getting much better. Perhaps we should re-examine the belief systems of our religious and medical institutions.

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North Carolina Medical Journal

Features for Patients January 1985

Home Care, An Alternative to Institutionalization:

Nurses in Action

Laura Lacy

At some time in our life, many of us may be forced to reach a decision regarding institutionalization versus home health care, for as we age so do our parents and grandparents.

Unfortunately, the majority of us have been unschaoled in the pro's and con's of each option.

Until the mid-1960s, institutionalization, regardless of appropriateness, was the accepted standard of health care delivery in the United States. Construction of facilities boomed, and with these beds available, nursing homes, convalescent centers, and retirement facilities sprang up everywhere.

At the first sign of illness or aging, in came the movers, out went the accumulated memorabilia of a lifetime and into a home went Mom. It did not seem to matter whether she liked it or not or even if she really belonged there. She was safe, well taken care of, and it was thought she would be able to live out her remaining years in comfort and security.

The revolt toward deinstitutionalization began when people started looking at the costs associated with this "confinement policy." Many began to listen to the home health care advocates' arguments on the social impact this situation was having and saw the morbidity statistics: the average patient confined to a nursing home lived in that environment a scant 19 months. Why? Was it because they had entered so very ill or, as many health care professionals believe, was it that their quality of life had changed so drastically that they no longer cared about living?

In light of these considerations, home care offered an attractive alternative to institutionalization. While in many instances the institution is the ideal situation, home care is and should be the ideal situation in others.

A home care program can mean many different things. As each patient has a differing need, the home care program must be developed to satisfy the individual's requirements. In many cases, companionship, meal preparation, and housekeeping services are the primary requirements.

The simplest definition of home health care is the provision of health care related services to persons in their place of residence. A home health care program can encompass many types of care. An evaluation of the person should be conducted which takes into account the diagnosis and prognosis, the patient's physical and social needs, diet, and therapy. The nursing implication should be assessed and determined and the availability of resources explored.

A comprehensive individualized nursing plan then should be tailored to meet the patient's requirements as indicated by the physician's plan of treatment. This care plan should detail the type(s) of service(s) to be provided, any equipment and supplies that may be required, and the level of personnel needed to perform the tasks. This could mean an R.N., L.P.N., home health aide, or physical therapist. A successful home care program must have one inherent component: it must be flexible and adjustable to satisfy the individual's changing needs.

While considerable attention has been directed at home health services for the elderly, a home care program can be tailored for anyone requiring direct or supportive assistance. A particular concern also may be the handicapped or developmentally impaired child who survives his parents, orphaned minor children, or a patient of any age who has a temporary or permanent physical ailment or limitation.

In most locations in North Carolina, there will be one or more home care providers available to carry out all these services. They are listed in the yellow pages of the telephone book. These offices are staffed by profes-

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sionals knowledgeable about Medicare, Medicaid and private insurance coverage who can inform the consumer of these facts.

In the United States, Americans are still struggling to discover the best way to care for dependent persons. The acceptance of the "new" home care movement appears to be dawning. William Buckley, author and columnist, is quoted as saying, "It has been widely acknowledged — though there are those who recognized the point — that the principal problem socially in America during the next 20 or 30 years is not going to be the problem of overpopulation, nor Soviet recklessness, nor nuclear war, but the problems of caring for the aged." In the past 20 years, we have increased by 10 years the predictable actuarial lifespan of the man who is 65 years old. As a result of heroic geriatric efforts, we have prolonged the efforts of our parents and grandparents to a point that is a tribute to our instincts to permit people to live as long as they can. But as so often happens, it is an instinct that does not face some of the complementary problems that go with it — the necessity of expanding home health care services.

There are times when it is appropriate for a person to be placed in a nursing home and other times when this placement is ill-advised. As no one wishes to see anyone prematurely institutionalized, responsible home care professionals do not advocate unrealistic home care programs. In the absence of a public long-term care policy, home health care providers have become committed to a community-based, in-home support service.

Consumers also have become committed to caring for their relatives (or themselves) within the home environment. The 1980s will see an even greater demand placed on nursing services for trained home care personnel. The size of our senior citizen population is rapidly growing; the costs associated with long-term confinement are skyrocketing while our nuclear family is shrinking; and previously full-time homemakers are entering the work place in droves. Home care remains a psychologically advantageous and cost-effective health care modality. Patients thrive and families benefit from a professionally developed, appropriately tailored health care program, relieving the burden faced by many families.

Helen Hayes, the noted actress and an outspoken advocate of home health care, recently appeared before the Senate Labor and Human Resources Committee to request federal aid for home care. The 81-year-old actress is quoted as saying, "The changes demanded by old age are tough to accept. Maintaining as much independence as you can makes it easier to yield gracefully to lengthened life. Now we must learn to make a longer life worth living. Older people deserve choices all over America, and we realize what we might have known from the start: for most of us, there really is no place like home."

The editor recently attended a conference on geriatric care sponsored by the Veterans Administration. Some 10 groups offering home health care services were invited to attend. Mrs. Lacy was the only one to respond. She contributed to the conference, and for this receives some free advertising in this issue of the *Journal*.

EAS

PRURITIS ANI

Claude S. Burton, M.D., Russell W. Eyre, M.D., and J. Lamar Callaway, M.D.

While it may be true that it is "better than riches to scratch where it itches," in the case of pruritis ani, or perirectal pruritis, such indulgence may be embarrassing. A careful observer of any large crowd will note that many among us suffer with rectal itching. Since not even television has ventured into this taboo but common public health problem, it is appropriate to do so in the medical journals. We hope our comments will be useful to many silent sufferers.

Pruritis ani is ordinarily a simple problem with a relatively simple solution. Though an occasional patient will have an infection (due to bacteria, yeast, or fungi), skin cancer, or coincidental involvement of another skin condition such as psoriasis or seborrheic dermatitis, the vast majority of cases relate to physical/mechanicol difficulties in the area. Invariably, there is some element of fecal soilage. Fecal contents are highly irritating to the sensitive skin around the anus. Even a small amount of fecal material when rubbed between the cheeks throughout a day of walking, sitting, and bike riding will produce irritation and itching of the surrounding skin. A brief walk on all fours suggests that this frictional problem is one of the consequences of our upright posture.

Fecal soilage has many causes. Loss of muscle strength in the perianal musculature will reduce the natural function of the anal sphincter or valve. Under pressure or gravity, inevitable fecal soilage occurs to the perianal skin. Trauma (childbirth, anal intercourse), neuromuscular disease (strokes, diabetic nerve damage), and mechanical problems often related to the presence of hemorrhoids, will interfere with function of this valve and lead to rectal leakage. Commonly, closely spaced hips and hair, especially in men, prevent adequate cleansing following defecation. The "single tissue" dispensers found in many public restrooms surely contribute to the problem.

In evaluating patients seen in our clinics with pruritis ani we routinely explore the regional anatomy to rule out mechanical and neuromuscular problems. Hemorrhoids may or may not require surgical therapy depending on the individual situation. Conservative care will usually suffice. A careful search for infection with bacteria, yeast, or fungi is routinely performed. At the same time we search for evidence of other skin diseases such as psoriasis. In many cases we ask the patients to obtain scotch tape preparations of perianal skin eorly in the morning to examine for the presence of pinworms. A history is taken to rule out the possibility of allergic contact dermatitis due to various topically applied medications, perfumes, etc.

The diet, which influences bowel function and stool composition for obvious reasons, is often a contributing factor. Stimulants contained in many soft drinks, coffee, tea and chocolate may have undesirable effects in patients with pruritis ani. Hot, spicy foods are occasionally implicated. Curiously, some foods which produce no allergic reaction in the bowel, such as cashew nuts, are relatives of the poison ivy plant and may produce a dermatitis when they reach the perianal skin.

The most important aspect of treatment is to keep the skin of the anal area clean and dry. In cases where extensive abrasion has occurred, prevention of further friction, rubbing and excessive wiping are mandatory. Many topical medications will only worsen the problem of moisture and irritation. Soaps are notorious for accumulating in this area and are highly irritating. We recommend that patients use water alone to clean the area when they shower. After bowel movements it is critical to remove all fecal contents. Wet cotton or tissue is better than dry toilet paper for this purpose and we find pre-moistened wipes such as Baby Fresh by Scott Paper Company a useful alternative. These may be carried in a baggie for use on the go. After thoroughly cleansing the area it is important to pat the area dry without rubbing. If you are the sort who notes leakage on your underwear then we suggest you wear a thin, cotton pledget applied directly to the anus between bowel movements. This should be small enough so that you are not aware of its presence. Consider thoughtfully your bowel habits. If you are the sort who ignores the call to nature until it is convenient, then you are undoubtedly contributing to the problem. If constipation is a problem, it should be addressed. An increase in fiber in the diet such as a bowl of Raisin Bran each morning is often all that is required.

The intensity of treatment varies directly with the severity of the problem. In some cases, topical steroid lotions are necessary to break the itch-scratch cycle. In others, a Prednisone taper may be necessary, particularly if topical therapy is irritating. In all cases, medication is part of an overall plan and not a substitute for the measures described above.

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The Top-Heavy Plan Rules: What Will They Do to Your Retirement Plan?

Walter R. Rogers, Jr. and Jennifer M. Dibble

• *A continuation of the retirement plan advice for physicians begun in the October 1984 NCMJ.*

I. Introduction

IN our last article we introduced the phrase "top-heavy plan" and promised to define it later. This article will discuss what "top-heavy" means and what effect being "top-heavy" may have on your present or contemplated qualified retirement plan.

Before the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA), tax law imposed stricter rules on retirement plans of unincorporated practices than on those of incorporated practices. Recognizing that this disparity in qualified retirement plans caused many professionals to incorporate their practices purely for tax reasons, Congress decided to equalize corporate and non-corporate retirement plans in most respects. TEFRA lifted some of the limits on non-corporate plans, primarily the lower contribution limits. However, TEFRA also extended many of the limits on non-corporate plans to all plans that provide greater benefits to certain, usually higher paid, groups of employees. These limits, along with others introduced by TEFRA, are the top-heavy plan rules. Thus, whether or not you have incorporated your practice, you must consider and respond to the top-heavy plan rules. In addition, whether or not your plan actually is a top-heavy plan, your plan documents must contain top-heavy plan language, which comes into effect if your plan becomes top heavy.

II. Definitions

As with most tax matters, the key to understanding the top-heavy plan rules is understanding certain terms that appear in the tax law.

A. "Top-Heavy Plan"

Almost any plan, whether a defined contribution plan such as a money purchase plan, or a defined benefit plan, can be a "top-heavy plan." A defined contribution plan is top heavy if the total of the accounts of key employees is more than 60% of the total of the accounts of all employees under the plan. A defined benefit plan is top heavy if the total value of accrued benefits of all key employees is more than 60% of the total value of accrued benefits of all employees under the plan. Certain plans of the employer are tested in the aggregate for purposes of the top-heavy determination. The definition of a top-heavy plan quickly leads to more questions. When is the top-heavy determination made? What is included in an account or in the definition of accrued benefit? Who is a key employee?

B. "Determination Date"

Each year an employer must determine on the "determination date" if its plan is top-heavy. The determination date is generally the last day of the preceding plan year or, in the case of the first plan year, the last day of the first plan year. The value of accounts and accrued benefits as of the determination date is the value determined on the most recent valuation date within the previous twelve months. The valuation date must be the same as the valuation date used for computing plan costs for minimum funding. Most plans will have the same valuation and determination dates.

A plan can theoretically change from top-heavy to non-top-heavy and back again as often as once a year. However, most physicians' plans are top-heavy, and are likely to remain so.

C. Accounts and Accrued Benefits

An employee's account in a defined contribution plan consists of all employer contributions made or due to be made on the employee's behalf to the plan as of the determination date, any income or gain on those contributions, and the employee's share of amounts forfeited by other employees leaving service before complete vesting. Accrued benefits in a defined benefit plan consist of the present value of benefits which would be paid to the employee upon retirement if the employee terminated employment on the date the accrued benefits are valued.

There are two additional categories of funds included in an account or in accrued benefits. First, all distributions to employees made within the last five plan years are added back into the account or accrued benefit. Second, all after-tax employee contributions, whether voluntary or required to be made under the terms of the plan, are included. Voluntary deductible employee contributions and certain rollovers from one plan to another are not included.

From the law firm of Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan, Box 12807, Raleigh 27605.

D. "Key Employees"

Congress devised the phrase, "key employee," in an attempt to include all persons who exercise some amount of control over an organization and presumably its retirement plan. Key employees are employees who are or were within the four preceding plan years, certain officers, a shareholder or partner owning a certain percentage of the employer, or one of the ten individuals owning the largest interests in the employer and earning more than $30,000 per year. (For plan years beginning after December 31, 1983, officers will not be key employees merely because of their status as officers unless they also have an annual compensation from the employer of more than $45,000.)

Most physicians will be key employees for purposes of their retirement plans. If the practice is incorporated, the physician may be a key employee because of being an officer earning more than $45,000. He may be a key employee because he owns more than 5% of all the stock or 5% of the stock voting power of the practice. He will also be a key employee if he owns more than 1% of the stock or stock voting power and receives more than $150,000 in annual compensation from the practice. If the practice is not incorporated, the physician owning more than 5% of the capital or profits interest of the practice, or more than 1% with more than $150,000 in annual compensation, is a key employee. A final catch-all category includes any of the ten employees who own the largest interests in the employer and earn more than $30,000 per year. The physician could be a key employee in more than one category but his account or accrued benefits will be counted only once each year in applying the top-heavy test.

There are two further refinements. First, certain "attribution rules" apply so that if, for example, a husband and wife practicing together each own 3% of the stock of the practice, each physician's stock ownership will be attributed to the other and both will be key employees owning more than 5% of the stock. Second, the beneficiary of a key employee is counted as a key employee. For example, if a key employee dies, the beneficiary receiving the key employee's account balance is counted as a key employee.

Perhaps the best way of putting the pieces together is to run through an illustration (table 1). Medical Practice, P.A. has three physicians. Drs. A and B each own 50% of the stock of the practice and therefore are key employees. Dr. C recently joined the practice and does not yet own stock or participate in the management of the practice. The practice has employed the same receptionist, a bookkeeper and two nurses since opening. In 1979 the practice established a money purchase pension plan with an annual employer contribution rate of 10% of compensation. All employees are eligible to participate from their date of employment. Plan assets have appreciated at a rate of 10% per year compounded annually. Employees have not contributed to the plan.

On the December 31, 1983 determination date Drs. A and B's accounts total $123,365.14. Since this is more than 60% of all employees' accounts, the plan is a top-heavy plan.

III. Consequences

As you can see from the example, a typical medical practice, with a small number of employees and a significant disparity between the physicians' and staff's salaries, is likely to have a top-heavy plan. The consequences of having a top-heavy plan are numerous. Some of the requirements of such plans affect all employees while others affect only key employees. In general, a top-heavy plan will be more expensive to maintain and offer less tax deferral to the physicians covered by the plan than a plan that is not top-heavy.

A. Vesting

The first requirement for a top-heavy plan is that it must adopt one of two vesting schedules. One choice is three-year vesting. Under this option all employees who have three years of service with the employer will have a nonforfeitable right to the portion of their accounts or accrued benefits derived from employer contributions. (Of course, an employee is always 100% vested in amounts derived from the employee's contributions.) The plan can exclude employees with less than three years of service from participation in the plan if it has three-year vesting, but as soon as employees participate they are 100% vested in employer contributions. The second type of vesting is six-year graded vesting. An employee is 20% vested after 2 years of service

Table 1

Employee	*Employment Date*	*Annual Compensation*	*Account Balance (Assuming Contribution and Appreciation of 10%/yr.)*
Dr. A	1/1/78	$100,000	$ 61,682.57
Dr. B	1/1/78	100,000	61,682.57
Dr. C	1/1/83	45,000	4,500.00
Nurse X	1/1/78	15,000	9,252.39
Nurse Y	1/1/78	15,000	9,252.39
Receptionist	1/1/78	10,000	6,186.26
Bookkeeper	1/1/78	10,000	6,168.26
Total			$158,706.44

and adds 20% per year of service until he is 100% vested at the end of six years. Which schedule you will want to adopt largely depends on your employee turnover rate.

Either of these vesting schedules probably favors employees more than most non-top-heavy vesting schedules. The effect of top-heavy vesting is to make a plan more expensive to the employer by reducing forfeitures. Forfeitures by employees who leave employment before being completely vested are redistributed among the remaining employees' accounts and generally reduce the employer's cost by reducing the amounts the employer must contribute to the plan.

B. Minimum Benefits

A top-heavy defined contribution plan requires minimum annual contributions on behalf of a non-key employee equal to the lesser of 3% of the employee's compensation or the percentage of compensation contributed on behalf of key employees. A top-heavy defined benefit plan requires minimum annual contributions in an amount sufficient to provide certain minimum accrued benefits for each non-key employee. The accrued benefits must equal an annual retirement benefit based on a percentage of the employee's average compensation for his five highest-paid years of service. The percentage is the lesser of 20% or 2% per year of service. Years in which the plan was not top heavy and pre-1984 years are not counted in the calculations. If an employer has more than one plan, it need meet the minimum benefit requirement in only one plan.

General plan qualification rules require that a uniform percentage of compensation be contributed or accrued on behalf of each employee, and most physicians who can afford to do so will want to contribute more than the minimum benefit amount on their own behalf. Therefore, most physicians' retirement plans are likely to already meet the top-heavy minimum benefit rules. One danger lies where a plan is integrated with Social Security, that is, where it includes Social Security payments or benefits in its contribution calculation. For example, a defined contribution plan may require no contributions on account of compensation up to the Social Security wage base and 5% contributions on account of compensation over the wage base. However, if the plan is top-heavy, Social Security benefits cannot be included in the minimum benefits calculation and the plan would have to be changed to require contributions of at least 2% of the non-key employees' entire compensation.

C. Annual Compensation Limit

A top-heavy plan must limit the amount of compensation taken into account in calculating contributions or benefits under the plan. For the present, no more than $200,000 of compensation per employee can be taken into account. Thus, a physician covered by a top-heavy defined contribution plan requiring 10% employer contributions can have annual contributions of only $20,000 made to his account even if he earns $300,000 from the practice each year. For the physician in this example to have the maximum annual contribution of $30,000 made on his behalf, the plan would have to require employer contributions of 15% of compensation (15% of $200,000 = $30,000). Of course, the employer would be required to contribute 15% of all covered employees' salaries, thus making the plan more expensive.

D. Plan Distributions

1. "Premature Distributions." A present or former key employee less than age 59½ who receives a distribution from a plan receives a "premature distribution." He will pay a 10% penalty tax on amounts attributable to contributions made on his behalf while he was a key employee in a top heavy plan. The tax will not be imposed in two situations: one, if the employee is disabled to the point of being unable to engage in any substantial gainful activity; and two, if the distributions are in the nature of a dividend to the policyholder of an annuity, endowment, or life insurance contract. The Tax Reform Act of 1984 (TRA) changes this rule effective January 1, 1985. After that date, employees who are or were "5% owners," rather than key employees, will be subject to the 10% penalty tax on all distributions from plans attributable to contributions made on their behalf while they were 5% owners. The same exceptions apply. A "5% owner" is an employee who directly or indirectly owns more than 5% of the stock, stock voting rights, capital or profits interest of the employer.

2. Required Distributions. TRA repealed the TEFRA provisions requiring full distribution of plan benefits to key employees by age 70½ or within their life expectancy. For now, pre-TEFRA law is in effect. Effective January 1, 1985, new rules will govern plan distributions. An employee must receive his entire interest by the later of the April 1 following the year he attains age 70½ or the April 1 following the year he retires. Alternatively, a plan must commence distribution by the later of those dates and complete distribution over (1) the life of the employee, (2) the lives of the employee and a designated beneficiary, (3) a period not extending beyond the life expectancy of the employee, or (4) a period not extending beyond the life expectancy of the employee and a designated beneficiary. However, under the new rules, the latest date by which a 5% owner can receive or commence to receive his interest is the April 1 following the year he attains age 70½ even if he has not yet retired.

E. Combinations of Defined Contribution and Defined Benefit Plans

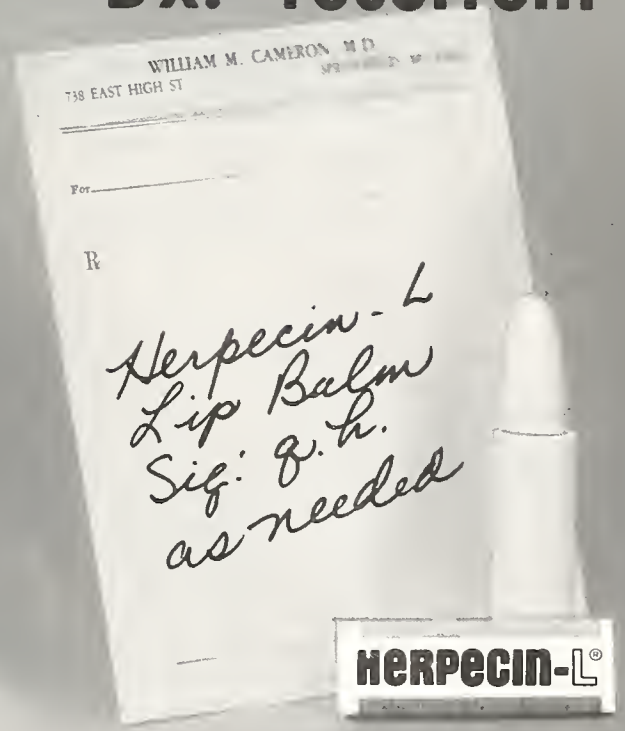
Generally, an employer can contribute more to a combination of defined contribution and defined benefit plans than it can to one or more defined contribution plans or one or more defined benefit plans. As a result, employees receive greater benefits from a combination of plans than they would otherwise receive. However, if one or more of the employer's plans is top-heavy, then the employer may lose the benefit of higher contribution limits that are in effect for a combination of defined benefit and defined contribution plans. First, the employer must test to see if one or more of his plans is "super top-heavy." If the accounts or accrued benefits of key employees in a plan total more than 90% of those of all employees, a plan is super top-heavy. In that event, the employer can contribute no more to a combination of defined contribution and defined benefit plans than it can to one or more defined

contribution or defined benefit plans. If the plans are not super top-heavy, but one or more is top-heavy, then unless the plan meets certain increased minimum benefit requirements (which will increase the employer's costs), the employer loses the advantage of combining plans.

IV. Conclusion

As you can see, a quick run-through of the top-heavy plan rules indicates that qualified retirement plans are likely to be less attractive to incorporated practices than they were before TEFRA. However, a qualified retirement plan still offers considerable tax savings while providing funds for retirement. Given the uncertainties of the Social Security system, the latter point has become important. Therefore, despite dire predictions of plan terminations after TEFRA, the qualified retirement plan will survive the top-heavy rules. Don't think, however, that once you have amended your plan to comply with TEFRA, you need do nothing further. Congress enacted two new laws affecting qualified retirement plans this year and once again plans must be amended.

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Julius Seizure — Carbamazepine (Tegretol) Poisoning

Ronald B. Mack, M.D.

• *How to care for the patient who took an overdose of CBZ.*

WHEN I was a young lad, my peers and I had heroes and heroines; in fact I still do. I don't know if the young people of today have anyone they want to emulate. With some of current celebrities that the youth of our country seem to admire it is hard to see whether these "notables" should be classified as heroes or heroines or, androgynously speaking, both.

Julius Caesar has always been one of my favorite historical figures — a real high achiever, a conqueror of men and, as it turns out, ladies — (three wives and a paramourship with the late, great Cleopatra — the Elizabeth Taylor of her era). During his lifetime, which lasted from 100 B.C. to 44 B.C., he was the Questor in Spain, Aedile, Pontifex Maximus (head of the state religion), Praetor, Governor of Further Spain, a member of the infamous Triumvirate — with the other two members being Crassus and Pompey — Consul and Governor of Cisalpine Gaul, Consul, Dictator and Imperator for life. [A *questor* managed the expenditure of state funds. An *aedile* was in charge of the care of buildings, aqueducts, theaters, saloons, brothels, etc.; a *praetor* was charged with the administration of civil justice; a *consul* was involved in the executive phase of peace and war (a chief magistrate); and an *imperator* was an absolute or supreme ruler.] He was a brilliant military leader and allegedly the second best orator of his time (Cicero won the Academy Award consistently in that department). Caesar performed all these feats even though he was handicapped; fact is, he was an epileptic. It is of interest that Julius' hero was Alexander the Great, another victim of the "falling sickness."

There are several historical references to Caesar's cerebral dysrhythmia, but one of the best, in my opinion, occurs in Will Durant's book *Caesar and Christ.*[1] In this wonderful text it is alleged that at the Feast of the Lupercalia in February 44 B.C., Mark Antony (reportedly drunk and naked) three times offered Caesar the crown of royalty. Three times Julius refused. Then the Roman Senate approached him as he sat in the Temple of Venus and Caesar remained seated. Let me make this perfectly clear — by custom he was supposed to stand up when greeting this august body. Why did he remain in his chair? Many witnesses claim he was overcome by an "epileptic stroke"; other witnesses say he was suffering from a bad case of the "trots" and remained seated to avoid an encopretic episode at so "unpropitious a moment." Another example where Kaopectate might have changed the course of history.

What happened to Julius that day? Did he forget to take his phenytoin or phenobarbital or carbamazepine — nay, nay, I say unto you, he was not taking any anticonvulsants as far as we know. Medicine until the third century A.D. consisted of family herbs, magic and prayer, for gods alone could heal. To ensure recovery the patient prayed to the specific god assigned to his/her specific disease. It is difficult to be historically certain about Caesar's religious beliefs (even though he was the religious head of the area) because he is quoted more than once as saying that no one can alter the plans of the gods, but on the other hand he seems to have been a believer in prophecy expressed through dreams. So much for history. By the way, what were we talking about? Oh yes — carbamazepine (Tegretol) henceforth known as CBZ in this epistle.

Now that the die is cast let us come and see and conquer the problem of CBZ overdose. This drug is structurally similar to the tricyclic antidepressants (oops, could this mean big trouble in overdose?) and is widely used in the treatment of major motor seizures such as grand mal and complex partial seizures as well as the drug of choice for trigeminal neuralgia (tic douloureux) and Lhermitte lightening pain syndrome (how many patients with this have you seen lately?). Apparently the drug works by inhibiting synaptic transmission of neural signals between two thalamic nuclei. The inhibition of the ventroanterior nucleus depresses efferent seizure discharge signals whereas inhibition of the centro-medial nucleus depresses afferent trigeminal pain sensation.

It is useful at this point to review some of the pharmacokinetics (Et tu, Brute?) of Tegretol because it might point the way to the management of the overdose event. After ingestion, the peak serum level is 3-6 hours in newborns, 1 to 8 hours in children and 8 to 24 hours in adults. At therapeutic blood levels (3-12 μg/ml) the volume of distribution (V_D) in newborn infants is 1-2 l/kg and 1-3 l/kg in children. About three-fourths of the plasma CBZ is bound weakly to protein. The metabolism of this drug is mainly hepatic and follows first order kinetics (rate of transfer of

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the drug is directly proportional to the amount of drug remaining). Of the several resultant metabolites only the *epoxide* has anticonvulsant properties. It is important to remember that the elimination half-life (T½) of CBZ and the epoxide ranges from 18 to 54 hours after a therapeutic dose, but only 16 to 26 hours for those patients on chronic Tegretol therapy because CBZ may induce its own metabolism via hepatic enzymes. What is of greater interest to those of us who treat overdose is the fact that the enzymes responsible for the oxidative metabolism of this drug do not seem to be saturable, hence no zero-order kinetics (elimination occurs at a fixed rate regardless of the amount of drug remaining) and thus the T½ is not prolonged in overdose. Chronic use of CBZ can have a profound effect on the metabolism of drugs taken contemporaneously. For example, chronic usage of CBZ decreases the T½ of oral contraceptives, coumadin, phenytoin and clonazepam probably because of microsomal hepatic enzyme *induction*. When ingested with propoxyphene or INH, however, there can be an increased CBZ effect because of microsomal hepatic enzyme inhibition with resulting CBZ intoxication. It has also recently been reported[2] that chronic CBZ ingestion can increase INH-induced hepatotoxicity.

Because Tegretol is structurally related to the tricyclic antidepressant imipramine, it is not surprising that an acute overdose can produce anticholinergic symptoms such as seizures, myoclonus, nystagmus, respiratory depression, ataxia, coma, mydriasis, delayed gastric emptying and tachycardia. The most severe clinical features are CNS depression with respiratory arrest. There is some good news in this otherwise bleak description — recalling only too well that the most common cause of death in most cases of tricyclic antidepressant overdose (not loxapine or amoxapine however) is cardiotoxicity with arrhythmias, etc., it's my pleasure to announce that life threatening cardiac events are only rarely a problem in CBZ overdose. Cardiorespiratory problems can occur of course, usually with serum CBZ levels exceeding 35 μg/ml.

Tegretol has at least one more weird potential property that must be mentioned — it may trigger Giles de Tourette's syndrome in susceptible patients at therapeutic levels of the drug. It has been argued that CBZ has a structural as well as functional structure similar to the phenothiazines and thus may act as a dopamine antagonist. Some investigators suggest that Tourette's syndrome may be the result of an augmentation of dopamine neurotransmission or an alteration in receptor functioning. Therefore in susceptible patients, CBZ acting on altered dopaminergic receptors may trigger the onset or exacerbation of Tourette's syndrome.

The treatment of carbamazepine overdose is fairly straightforward — there are no antidotes and management is mainly supportive, i.e., treat the patient, not the poison. There are some tricks however. Because of the anticholinergic-like action of the drug, delayed gastric emptying is often present with impairment of absorption of the drug. Another fact worth noting is that CBZ can easily form a drug concretion when ingested in quantity in an overdose situation. What this implies to the people who manage such an overdose patient is that gastric emptying is indicated for many, many hours post ingestion, e.g., for as long as 12 hours or more in asymptomatic patients and up to 60 hours in symptomatic patients. Metoclopramide has been used to increase gut motility. *Activated charcoal* can really make a big dent in the absorption of the drug and dramatically reduce the T½ if given repetitively with a saline cathartic. Repeated charcoal and cathartic administration seems to be indicated until the serum CBZ level decreases or there is clinical evidence of improvement. In my recent experience, this type of management works quite well. Fluid diuresis does not work here and is dangerous because CBZ can augment ADH secretion. Hemodialysis and peritoneal dialysis do not appear to be effective in CBZ overdose. Physostigmine has been used to combat the anticholinergic-like effects but this method has been unsuccessful and should probably not be used in this overdose. Charcoal hemoperfusion has been suggested as an option in severely intoxicated patients but experience is very limited with this method.

In Shakespeare's classic work about our hero, there are two characters named Cinna; one is a conspirator who lures Brutus into the plot to eliminate Caesar and the other is Cinna, a poet. The poet is killed on the way to Caesar's funeral. After Mark Antony's funeral oration there is a riot inspired by the speech and the mob confuses our hapless poet with his namesake, Cinna the conspirator. After pleading innocent to the conspiracy charge, the poet is killed by the mob anyway — it is alleged, "for his bad verses." Now that is a frightening prospect. Do not be surprised if my articles are by-lined with a nom de plume from now on. Please be careful out there — the ides of March is soon upon us.

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American Association of Poison Control Centers Certifies the Duke Program: The End of a Long Odyssey

Shirley K. Osterhout, M.D.

• *The Duke Poison Control Center comes of age.*

WHEN Jay Arena organized the Duke Poison Control Center in 1954, life was still relatively simple. This first Center in North Carolina and the second in our country received about 100 calls a year and most of the inquiries were about aspirin. The information in the Center was compiled by Arena and a few of the pediatric residents. The newly organized National Clearinghouse of Poison Control Centers of the U.S. Public Health Service provided without charge excellent and up-to-date card files. Funds from the Department of Pediatrics were used to purchase the half-dozen books on toxicology available at that time. There were no poison control journals.

Arena's secretary and the secretary of the pediatric resident kept the medical record of each case on file cards. There was no paid staff.

By the mid-1960s we were rapidly expanding our information base. There were more available textbooks and books providing product and ingredient information. As our reputation spread as a good information source, not only did our calls increase — requiring the production of more reporting cards — but our written replies to letters resulted in a heavier clerical load. The increased activities added to the cost.

The North Carolina Department of Human Resources, Maternal-Child Health Branch, developed an interest in us and provided funds to the Department of Pediatrics to help with some of the basic needs for 1970-1983. These funds allowed us to develop our own office, hire a secretary, buy a dictating machine, typewriter and file cabinets. All supplies, postage, and telephone bills were paid with these monies. More and more people requested information in the form of pamphlets and brochures and more of these became available — many free, but many had to be purchased. Again, this became a line item in our budget for North Carolina. As our reputation grew, so did the demand for speakers. Each year more invitations were accepted away from Durham to give programs and health fairs. Another addition to the budget was funds for travel. As our services increased so did the State support — up to approximately $40,000 a year until 1980.

From the Duke Poison Control Center, Durham 27710.

During these years the Maternal-Child Health Branch allowed us to survive and grow, while asking very little of us in return. We served as the unofficial state consultant to various agencies and boards. We reviewed written material that came to them and answered letters regarding various phases of toxicology. Each quarter we submitted a financial report and, at year's end, a written report regarding our statistics. Our working relationship with them was pleasant and my opinion of these individuals, especially of Dr. Jimmie Rhyne, cannot be expressed in words.

After several discussions with representatives of the N.C. Office of Emergency Medical Services of the Division of Facility Services, in the spring of 1978 I undertook a "first" for me — writing a grant proposal, which was the first of several to be submitted to them each year. Starting in 1978 and spreading over the next three years, the Office of Emergency Medical Services provided us $130,000. This combined funding, however, proved to be a piecemeal effort toward meeting and maintaining the standards that had now been set forth by the American Association of Poison Control Centers.

We made several applications to the American Association of Poison Control Centers for certification and met all the criteria except two. The first required that the State recognize Duke as a regional center. The State did not wish to designate us as a regional center until we were certified by the American Association of Poison Control Centers. The second requirement was that only "poison information specialists" or "poison information providers" take our calls rather than pediatric resident physicians. The purpose of this is to provide someone whose entire effort is at the disposal of the Poison Control Center.

As defined by the American Association of Poison Control Centers, a poison information specialist is someone qualified to read, understand, and interpret standard poison information resources and to transmit that information in a logical, concise, and understandable way to both health professionals and consumers and to transmit standardized poison center treatment protocols which have been approved by the medical director. This requirement is considered to be met if the person has a degree and/or is qualified for licensure in nursing, pharmacy, or medicine, or equivalent training experience plus training and/or ex-

perience in toxicology and poison information services. The Association's definition of a poison information provider is exactly the same except that there is no requirement for a degree other than that the person have an appropriate health-oriented background and specific training and/or experience in poison information sciences. We now have poison information specialists and providers who are with us 24 hours a day in all shifts, seven days a week.

The qualifications we have looked for in hiring these people go beyond the definition that the American Association of Poison Control Centers gives, in that we do not want someone who can merely read or give information; we want someone who can also communicate successfully on a personal and caring basis, who can be reassuring to the lay public, who can work in a counseling and training capacity, and who is diligent and reliable. We have advertised and had many applicants for these jobs. I have found that a degree in nursing or pharmacy does not necessarily give one the qualities we are looking for. Some certified emergency technicians who have the qualifications recommended by the AAPCC also meet my own standards. Currently we employ three registered nurses; a pharmacy technician who has worked as a licensed practical nurse and as a Navy corpsman with 20 years of clinical experience in hospitals; two college graduates who are enrolled in the Physician's Assistant school at Duke who are certified emergency medical technicians, one of whom is a certified poison information specialist, having worked at a poison control center in Maine; and a Duke graduate with a B.A. in chemistry who began working with the Center as a data computer technician in 1979 and has proved that bright, non-medical people can be taught and can provide all the qualifications we demand. We have allowed these people to assist outside the Center in nonprofessional training and have encouraged them to take examinations to certify themselves as poison information specialists. A continuing education program is given to them so they will maintain an interest in current changes in toxicology and the treatment of specific problems. They have been trained for their jobs by me and by Assistant Director Richard Drew and have also learned from each other. The starting salary is approximately $8 per hour.

In many ways they are far superior to the pediatric senior residents in that working in the Center is 100% of their job, with no responsibilities at any other outside task. Since their interest is in toxicology, their reading and education are confined primarily to this role so that their knowledge in toxicology is greater than that of the pediatric residents. With no other responsibilities, they are able to take far more time with each call, provide better followup, help review material that might need to be sent to the caller, such as protocols, and arrange transport from one area to another. I have been impressed also by the counseling job they are able to do in the area of poison prevention to the average family as well as counseling in the area of suicide attempts.

Because of financial limitations, Emergency Medical Services was not able to continue our funding at the end of June 1982, and again we had to rely entirely on the Maternal-Child Health Branch of the State Division of Health Services. These funds were minimal compared with what they had been in the past but private funds were found by the Duke University Medical Center Development Office and we remained alive. In January 1983 we received a sizable grant from a private source which enabled us to continue use of our toll-free number and our poison information specialists. We were pleased that what we were trying to accomplish and what we had accomplished were important enough for the private sector to have faith in helping us continue.

In February 1983 a group from Duke Medical Center representing the administration and the Department of Pediatrics met with officials of the N.C. Department of Human Resources, Maternal-Child Health Branch, and Emergency Medical Services. A budget was submitted for what was felt to be the basic needs of the Poison Control Center, which would also satisfy the requirements for certification. A proposal was put together by the staff of the Department of Human Resources under the direction of Dr. Ronald H. Levine to support a statewide poison control center.

In the spring of 1983, Senator Kenneth Royal (D-Durham) filed a bill which was passed by the General Assembly appropriating $360,000 to the Department of Human Resources for the establishment of a statewide poison control and information center. After several months of review, the Department of Human Resources awarded the contract — $180,000 for 1983-84 — to Duke to continue to operate a poison control center and to establish itself as the regional center for North Carolina.

We initiated an outreach program to all hospitals registered with the North Carolina Hospital Association, licensed day care centers, county health departments and community Head Start programs. We have redone the computer program which had been on hold since 1981 for financial reasons and hope we can again achieve an appropriate data collection and instant reporting system for those who need immediate up-to-date statistics. These funds will also help us to enlarge our current poison center library with information not only to cover the most common type of call we receive — that is, for acute exposure — but also to provide information on occupational and environmental hazards, drug interactions, fetal drug problems, and certain consumer issues. We have continued to publish a brochure, *Poison At Work,* and now are also able to provide a small card that can be carried in a wallet or purse or attached near a phone. I feel that one of the best things we can do with this money is to provide information on request to the individual citizen of North Carolina. We have many types of brochures, including material on plants, holiday hazards, pesticides, and even a "poison game" to teach safety to children. Although we have usually tried to accommodate requests from a community to give programs in hospitals, schools or civic organizations, we had been limited in the past several years due to lack of travel funds. We now look forward to such requests. Emergency Medical Services has approved a budget to endorse public education and we are far more available to travel into a community and give programs to both medical professionals and nonprofessional groups. Not a day in February 1984 went by without at least two requests for educational material. Our activities have increased markedly!

In November 1984 Duke was certified as a poison control center by the American Association of Poison Control Centers. Our long odyssey had ended.

We welcome the opportunity to continue to work with the State. We now have the resources to reach the entire State. We can answer questions on acute and chronic exposure and provide information on treatment. Even more importantly, we can move forward in prevention.

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Lewis gets to the heart of the matter

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The Role of Oxygen Pressure in the Fight Against the Chief Killers in the First and in the Last Half of the 20th Century

Barbara Newborg, M.D.

• *The fashionable therapies for tuberculosis patients used earlier in this century had a common physiological effect: they reduced oxygen pressure which in turn inhibited the oxidative processes of the tubercle bacillus.*

WHY were patients with tuberculosis, the chief killer until the 1940s, urged to have maximal weights?

The accepted dietotherapy for patients in the tuberculosis sanitariums consisted in giving large amounts of butter, cream, eggs, cheese and other high caloric items to promote all possible weight gain. The plausible explanation was that, due to the chronic fever, the patients burned up more calories and unless they were overfed they would die of "galloping consumption."

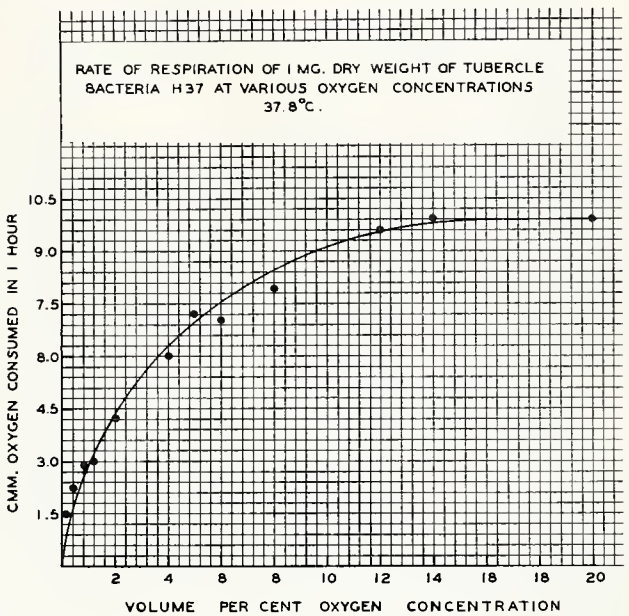
The second fashionable and obviously helpful treatment was sending the patients to high altitudes, the explanation being that the air was purer there and there was more ultraviolet light.

The third type of treatment that had proved successful was pneumothorax, or cutting the phrenic nerve to elevate the diaphragm, or rib resection. The explanation here was that thereby the affected lung tissue was given less work to do and more rest.

After the discovery of antibiotic therapy these forms of treatment were almost relegated to books about the history of medicine. However, from a scientific point of view it was interesting to establish the physiological rationale of these therapies.

In 1939, W. Kempner published a paper about "Oxygen Tension and the Tubercle Bacillus" in the *American Review of Tuberculosis,* in which he reported that contrary to Warburg's "all or nothing law" of cellular respiration, a considerable decrease of the oxidative processes of the tubercle bacillus was found under conditions of lowered oxygen pressure (figure 1).

Since these oxidations are virtually the only energy-supplying mechanism of the tubercle bacillus, its power to harm would be greatly inhibited by conditions like high altitude, pneumothorax, etc., which lower the oxygen pressure at the site of the infected tissue.



But what has this dietotherapy, the insistence on maximal weight, to do with high altitude and pneumothorax?

We have determined* the oxygen pressure in the arterial blood of 105 overweight patients before and after a period on a weight reduction diet. While some of the patients had no complaints except their overweight, quite a few showed symptoms of narcolepsy, lack of alertness, failing memory, impotence, inability to burn calories, etc., which improved with the weight reduction. The outcome of the determinations was an average increase of the oxygen pressure in the arterial blood from 71.1 to 81.4 mmHg after an average weight loss of 49 pounds in an average period of 100 days. (Incidentally, the chest films of obese patients

From the Department of Medicine, Duke University Medical Center, Durham 27710.

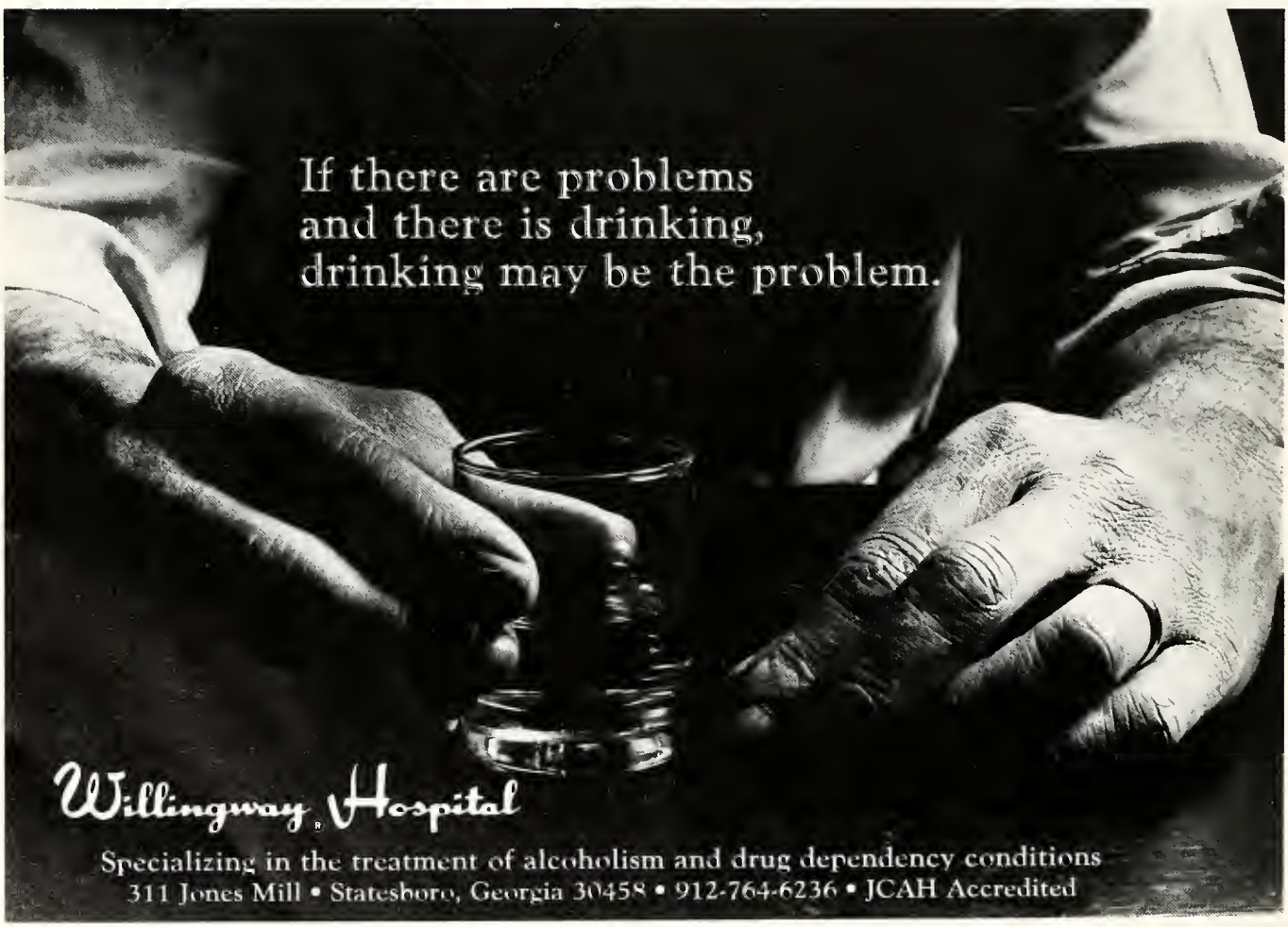
* Barbara Newborg, Fed Proc (Physiology) 1977; 36.

often look like those of patients with bilateral artificial pneumothorax: see *North Carolina Medical Journal,* page 242, April 1983.)

This shows that the practical approach of the dietotherapy of maximal feeding in tuberculosis had the same physiological basis — the decrease of oxygen pressure — as that of high altitude and pneumothorax therapy, though a quantitative explanation was not available at the time it was advised. One is reminded of what E. A. Stead wrote in 1978 in a paper about "Holistic Health": "It is sounder to determine by proper observation whether the treatment is beneficial. If it is, rationale will be developed in time to make the venture fit into the mold of biologic science."

If the bacteriostatic therapy which we are lucky enough to have now at our disposal did not offer so much better means to kill the tubercle bacillus, the treatment by decreasing the oxygen pressure would probably still be the most efficient.

With regard to tuberculosis, oxygen pressure is no longer of paramount importance. It remains, however, one of the most decisive factors in another therapeutic approach, though exactly in the opposite direction: today we are faced with the task not of *decreasing* but of *increasing* the oxygen pressure in the body in our fight against the chief killer of *our* time, the so-called cardiovascular diseases in which a decrease of oxygen pressure in the cells, for instance by overweight, has occurred, not only in the case of intermittent claudication of the leg muscles but also in the intermittent or permanent claudication of the testes, the kidneys, the myocardium or the brain.



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Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

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Avulsion Injuries of the External Ear

George W. Weston, M.D., J. Connell Shearin, M.D., and Anthony J. DeFranzo, M.D.

- *Even the completely amputated ear can be successfully reattached if it is preserved and brought to the plastic surgeon.*

AVULSION or partial avulsion of the external ear may occur secondary to animal or human bites, motor vehicle accidents, and many other sources of trauma, and it results in a wide variety of disfiguring defects. Although most cases are ultimately treated by a plastic surgeon, the primary care physician, by properly salvaging the avulsed portion, can play an important part in the successful outcome of this injury.

Case Material

Three patients with partially avulsed ear injuries have been treated at Wake Forest University Medical Center in the past 12 months: a 63-year-old man who was thrown from a horse (figures 1 and 2); a 38-year-old woman who was bitten by a horse (figures 3, 4 and 5); and an 8-year-old boy who was bitten by a dog. All three patients were treated within 12 hours of injury by reattaching the avulsed part and burying that part, if needed, beneath a retroauricular skin flap.

Discussion

Since the early 1500s, surgeons have attempted replantation and reconstruction of the avulsed auricle, but only since the 1950s have modern techniques made the results fully acceptable. Techniques for preservation and use of denuded cartilage from the avulsed ear have been advanced by many authors;[1-3] in 1971, Mladick and co-workers[4] first reported success using superficial dermabrasion, reattachment, and pocketing of the denuded cartilage beneath a postauricular skin flap.

The salvage procedure selected by the plastic surgeon depends upon the size and location of the avulsed part, the source of the injury, and the condition of the remaining tissues. Simple replantation of large composite parts will almost certainly fail, and reconstruction should only be attempted by surgeons familiar with the problems that may be encountered.

As in any other avulsion injury, collection and preservation of the avulsed part cannot be overemphasized. Although satisfactory reconstruction can be performed by fabricating a new auricular framework from costal cartilage or contralateral auricular cartilage, salvage of the avulsed segment can greatly simplify the reconstruction and improve the results: The number of surgical procedures required is fewer when the avulsed auricular cartilage is used;



Figure 1. *Near amputation of right helix and scapha in a 63-year-old man who fell from a horse. Blood supply from the inferior pedicle allows viability with simple reattachment.*



Figure 2. *Result three months after injury.*

From the Section on Plastic and Reconstructive Surgery, Department of Surgery, Bowman Gray School of Medicine, Winston-Salem 27103.

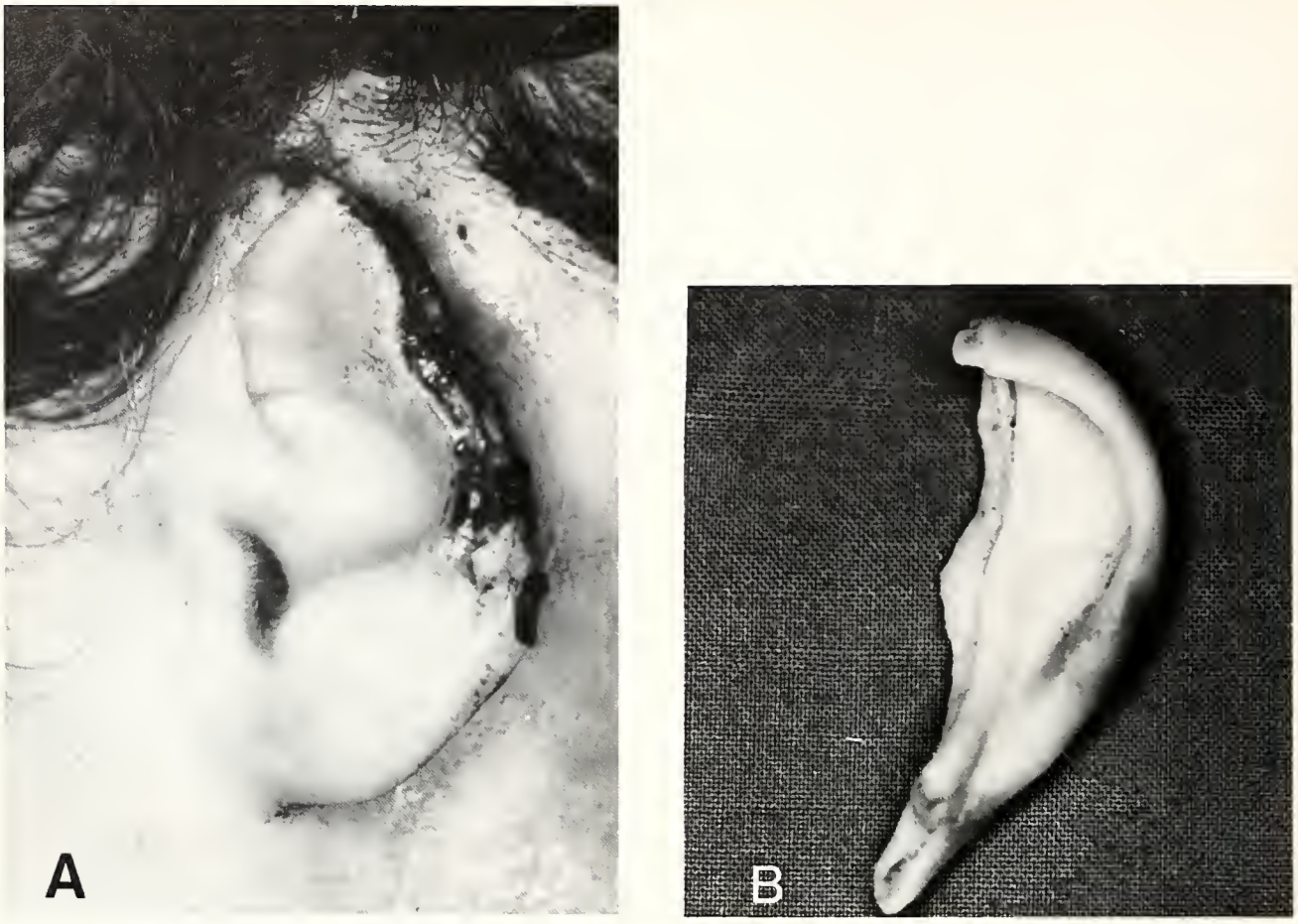


Figure 3 (A and B). *Amputation of the middle and upper half of the left helix and scapha of a 38-year-old woman secondary to a horse bite.*

the ear framework is more delicate; and the result looks more natural.

The retrieved avulsed part should be cleansed of any gross contamination with saline, wrapped in a sterile penicillin/saline sponge, and placed in a polyethylene bag. It should then be placed on regular ice, but separated by a single layer of sterile towel to prevent freezing. Hemorrhage from the site of injury can usually be arrested by application of a bulky pressure dressing. Prophylactic antibiotics such as penicillin or a cephalosporin should be started, tetanus immunization given (or updated if necessary), and adequate analgesia achieved before the primary physician refers the patient to the plastic surgeon.

The plastic surgeon first evaluates the surrounding tissues, particularly the retroauricular area, and then assesses the avulsed part. If the ear remains attached even by a small pedicle of tissue, survival is often possible with simple reattachment (figures 1 and 2). This is not possible if the avulsion is complete (figure 3). With complete avulsion, if the regional cutaneous tissues and the avulsed part are in good condition, the cartilage of the avulsed part is stripped of skin, reattached, and then buried beneath a retroauricular skin flap (figure 4). If retroauricular implantation is not possible because of injury to this area, the cartilage can be "banked" subcutaneously in a cervical pocket, and then transferred to the retroauricular area once wound healing is adequate. Antibiotics are continued for 7 to 10 days. Three to six weeks after the initial replantation, the auricle is elevated with the skin flap attached, and the retroauricular sulcus is created with full-thickness skin grafts. If needed, "touch up" procedures using available local tissues can be performed later under local anesthesia (figure 5).

In summary, reconstruction of the amputated ear is simplified, surgical complications are fewer, and the cosmetic results are improved whenever the amputated part can be preserved and used in the reconstructive surgical procedure.

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Figure 4. *Replantation of auricular cartilage covered with a postauricular skin flap.*

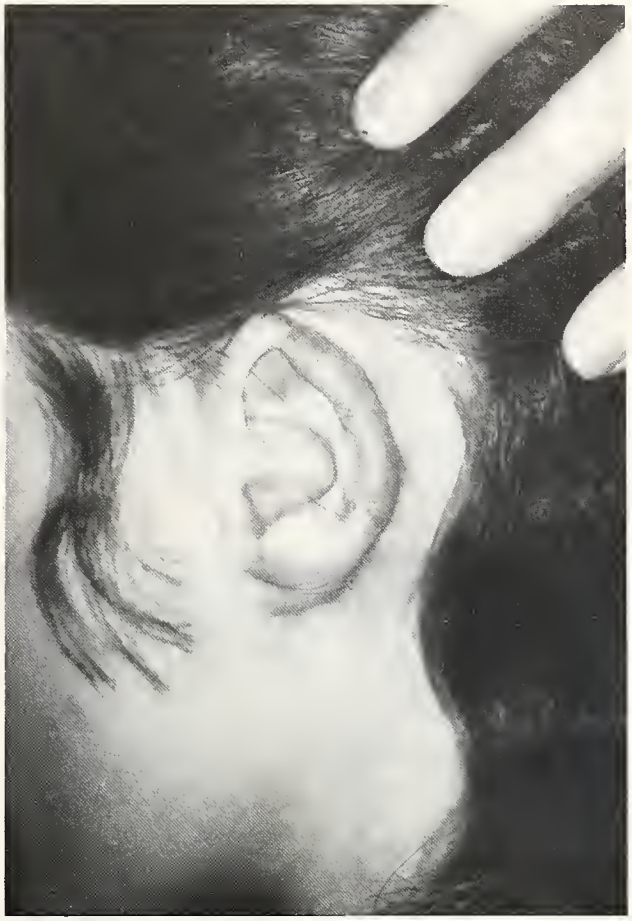


Figure 5. *Final result one year after injury following skin grafting to create the postauricular sulcus.*

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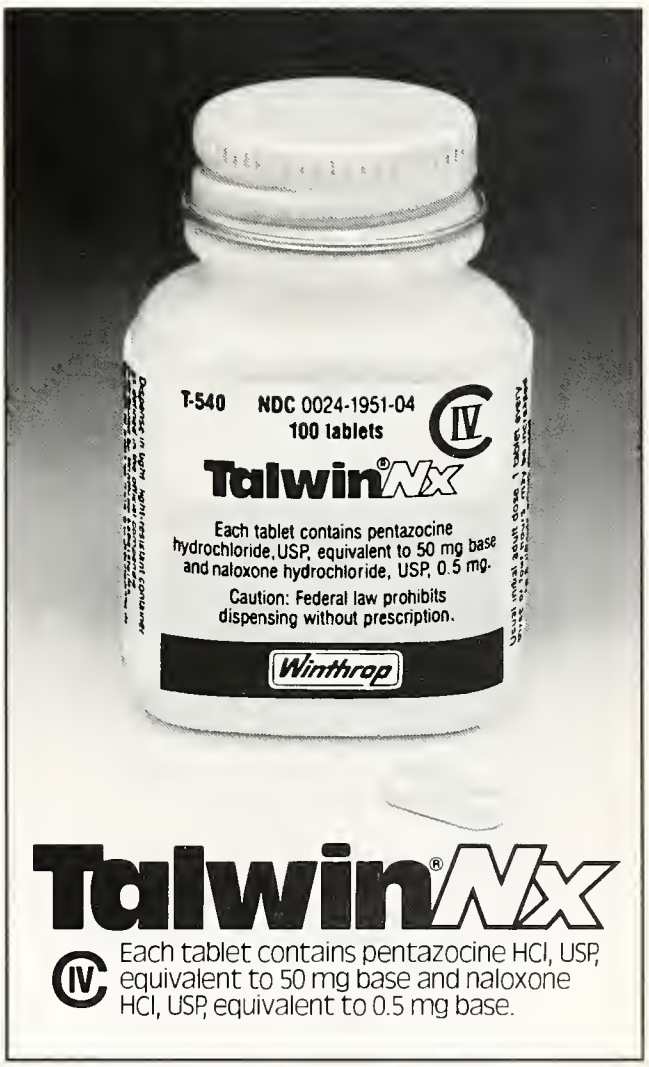
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No longer do doctors have to deny patients the benefit of an effective oral analgesic for fear of its misuse by injection.

Winthrop-Breon Laboratories has met a nagging problem by reformulating TALWIN® 50 (pentazocine HCl tablets) with the addition of naloxone, equivalent to 0.5 mg base. The reformulated product is called TALWIN® Nx.

The original formulation had been subject to a form of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ,* an antihistamine, would be ground up together, put into solution, and injected intravenously. The combination produced a heroin-like high. Because naloxone is a narcotic antagonist when injected intravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine in a combination of TALWIN Nx and PBZ. When taken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for the relief of moderate to severe pain, now providing added security against misuse.

*Registered trademark of Ciba-Geigy Corp for tripelennamine.



The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

Winthrop-Breon

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Please see following page for Brief Summary.

Talwin® Nx® IV

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone.

TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence.* Can cause physical and psychological dependence (See **Drug Abuse and Dependence**.) *Head Injury and Increased Intracranial Pressure.* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Can obscure the clinical course of patients with head injuries; in such patients, use with extreme caution and only if deemed essential. *Usage with Alcohol.* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics.* Pentazocine is a mild narcotic antagonist. Withdrawal symptoms have occurred in patients previously given narcotics, including methadone. *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Precautions: *CNS Effect.* Use cautiously in patients prone to seizures; seizures have occurred though no cause and effect relationship has been established. Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours. Such patients should be very closely observed and vital signs checked; if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function.* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient. *Biliary Surgery.* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures; the clinical significance of these findings is not yet known. *Information for Patients.* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction.* Use with caution in patients with myocardial infarction who have nausea or vomiting. *Drug Interactions. Usage with Alcohol.* See **Warnings**. *Carcinogenesis, Mutagenesis, Impairment of Fertility.* No long-term studies in animals to test for carcinogenesis have been performed. *Pregnancy Category C.* Should be given to pregnant women only if clearly needed. *Labor and Delivery.* Use with caution in women delivering premature infants. Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown. *Nursing Mothers.* Caution should be exercised when administered to a nursing woman. *Pediatric Use.* Safety and effectiveness in children below the age of 12 years have not been established.

Adverse Reactions: *Cardiovascular:* Hypotension, tachycardia, syncope. *Respiratory:* Rarely, respiratory depression. *CNS Acute CNS Manifestations:* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted. *Other CNS Effects:* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor. *Gastrointestinal:* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress. *Allergic:* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora. *Ophthalmic:* Visual blurring and focusing difficulty. *Hematologic:* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance.* TALWIN Nx is a Schedule IV controlled substance.

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported. In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient. Tolerance to the analgesic effect is rarely reported; there is no long-term experience with oral use of TALWIN Nx.

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine; however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics. TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Overdosage: *Treatment.* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing.

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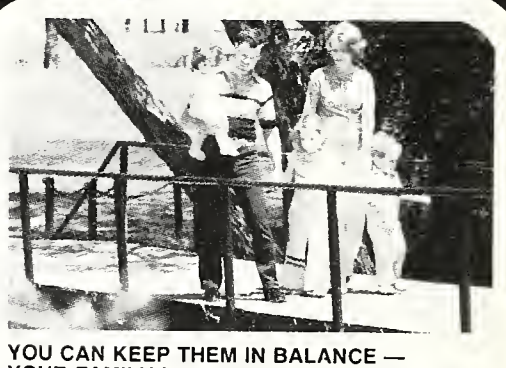
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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

January 7-March 1
Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 23
Wills, Trusts and Estate Planning for the Physician and Family
Place: Sanford
Credit: 2.5 hours Category I AMA
Info: R. S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

January 26
Sixth Annual Pulmonary Disease Update
Place: Greenville
Credit: 6 hours Category I AMA
Fee: $60.00
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

February 6
Grief Process in Children
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winson-Salem 27101-2482. 919/723-3571

February 13
Anxiety Disorders
Place: Greenville
Fee: $30
Credit: 3.5 hours
Info: Mary Valand, Box 7224, ECU, Greenville 27834. 919/758-5200

February 17-20
Improving Residency Rotations: Curriculum Planning and Negotiations
Place: Rougemont
Credit: 20 hours Category I AMA, AAFP
Info: Dr. Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 18-20
Selected Topics for the Practicing Clinician
Place: Durham
Credit: 24 hours Category I AMA, AAFP
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 6
Eating Disorders of Childhood and Adolescence
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

OUT OF STATE

January 17-19
Advanced Ultrasound Seminar
Place: Orlando, FL
Credit: 14 hours Catetory I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 22
38th Annual Stoneburner Lecture Series: Rehabilitation Medicine
Place: Richmond, VA
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

January 25-27
Winter Conference on Geriatrics
Place: Hot Springs, VA
Credit: 10 hours AAFP prescribed
Fee: $100
Info: NC Academy of Family Physicians, Box 20146, Raleigh 27619

January 26-31
Dermatology for Non-Dermatologists
Place: Cancun, Mexico
Info: Division of Dermatology, Box 3135, Duke University Medical Center, Durham 27710. 919/684-2504

January 27-February 2
Surgical Management of Malignant Disease
Place: Vail, CO
Credit: 25 hours Category I AMA
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

February 3-8
Selected Topics in Internal Medicine
Place: Snowshoe, WV
Credit: 20 hours Category I AMA and AAFP
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878

February 3-8
Sports Medicine for the Primary Care Physician
Place: Snowshoe, WV
Credit: 20 hours Category I AMA and AAFP
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878

February 4-6
Winter Retreat: Pulmonary Medicine
Place Wintergreen, VA
Fee: $250
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

February 16-23
Radiology Postgraduate Course
Place: Ixtapa, Mexico
Credit: 25 hours Category I AMA
Info: Jackie Wright, Box 3834, DUMC, Durham 27710. 919/681-2711 ext. 285

February 24-28
Duke Aging Symposium
Place: Palm Beach Gardens, FL
Credit: 15 hours Category I AMA
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 4-7

Interventional Techniques and Radiologic Management of the Emergency Patient
Place: Williamsburg, VA
Fee: $425
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 16

Reconstructive Plastic Surgery
Place: Richmond, VA
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 29-31

Ophthalmology: Cataract Surgery and Intraocular Lenses
Place: Williamsburg, VA
Fee: $275
Info: Kay Parrott, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

New Members

BUNCOMBE

William Maurice Huffstutter (CHN), 50 Doctor's Drive Ste. 210, Asheville 28801

CUMBERLAND

Catherine Herlihy Beyer (PD), 1213 Walter Reed Road, Fayetteville 28305

John Frederick Blue, Jr. (FP), 4092 Professional Drive, Hope Mills 28348

Paul Sheldon Johnson (P), 302 Thorncliff, Fayetteville 28303

DURHAM-ORANGE

Frederick Barton Askin (PTH), Surgical Pathology, Box 27, N. C. Memorial Hospital, Chapel Hill 27514

Michael Bryan Caveness (Student), 107-A Tall Oaks Road, Chapel Hill 27514

James Norman Davis (N), Neurology Section, Durham V. A. Medical Center, Durham 27705

Fred Daniel Koch (Student), 3207 Myra Street, Apt. H, Durham 27707

James Edward Lowe (CDS), Box 3954, Duke Univ. Med. Ctr., Durham 27710

Richard Lucas McCann (GS), Box 2990, Duke Univ. Med. Ctr., Durham 27710

George William Rozakis (Resident), 2 Abingdon Way, Durham 27707

FORSYTH-STOKES-DAVIE

Joseph MacDonald Ernest, III (OBG), Dept. of Ob-Gyn, Bowman Gray School of Medicine, Winston-Salem 27103

Robert Glenn Hornbeck (Student), 1900 Queen Street Apt. A-7, Winston-Salem 27103

Billy Ray Hunter, P. O. Box 2648, Winston-Salem 27102

William Sherwood Kelly (FP), 2031 Academy Street, Winston-Salem 27103

Donald Kenneth Matthews (Student), 1900 C-4 Queen Street, Winston-Salem 27103

GUILFORD

Philip Jerome Karam (FP), 439 W. Swannanoa Avenue, P. O. Box 1477, Liberty 27298

HALIFAX

James Russell Dykes (FP), Route #1, Box 287, Roanoke Rapids 27870

JACKSON

James Clayton Smallwood (OBG), Eastgate Medical Building, Sylva 28779

LEE

Roger Wilbert Anderson (OTO), 1911 K. M. Wicker Drive, Sanford 27330

LENOIR-GREENE

Roy Nathan Everett (PUD), 109 Airport Road, Kinston 28501

MECKLENBURG

John McNeill Gibson (IM), 1029 Churchill Road, Box 207, Davidson 28036

Arlene Rae Martone (OBG), 1012 S. Kings Dr., Ste. 306, Charlotte 28283

NEW HANOVER-PENDER

Boyd Keith Bresnahan (P), 2023 South 17th Street, Wilmington 28401

ONSLOW

Richard Grant Smith (OTO), 124 Epworth Drive, Jacksonville 28540

Larry Brent Wilshire (OPH), 264 Memorial Drive, Jacksonville 28540

PASQUOTANK-CAMDEN-CURRITUCK-DARE

Paul Andrew Kizen (OBG), 1142 N. Road Street, Elizabeth City 27909

PITT

Bela Laroia Aneja (Resident), 210 Churchill Drive, Greenville 27834

Roberta Skinner Gray (PNP), Dept. of Pediatrics, ECU School of Medicine, Greenville 27834

Robert Willard Olds, Jr. (P), 3005 Briarcliff, Greenville 27834

Mark Lucas Phillips (IM), Dept. of Medicine, ECU School of Med. Room 389, Greenville 27834

Jose Miguel Risco (OPH), 107 Lord Ashley Drive, Greenville 27834

ROWAN

George Raymond Everhart, III (FP), 201 Woodson Street, Salisbury 28144

VANCE

Young Hwan Ko (AN), 2131 Coleman Place, Henderson 27536

WAKE

Barry Alan Bruggers (OBG), 121 Edinburgh South, #103, Cary 27511

Timothy Bertrand Hart (IM), 1212 Cedarhurst Drive, Raleigh 27609

James Arthur Mong (OBG), 100 S. Boylan Avenue, Raleigh 27603

Rafael Mariano Moreschi (IM), 530 Loch Ness Lane, Cary 27511
Joseph Walter Sledge, III (IM), 1157 Executive Circle, Cary 27511
Pamela Joyce Whitney (N), 3320 Executive Drive, Raleigh 27609

In Memoriam

WILLIAM K. NELSON, M.D.

Dr. William K. Nelson was born October 16, 1944 and died June 5, 1984. He is survived by his wife Camille, sons Doug and Jeff, and mother Jane. Dr. Nelson's dedication to his profession and patients was absolute. His caring and concern for his patients was exemplary. In return, he was loved by those he cared for.

He loved sports, and was a sportsman in the truest sense. He loved and studied the game of golf, and was a tough competitor on the squash courts. He was a Wake Forest graduate and followed Wake sports with the enthusiasm of a diehard.

Dr. Nelson was an active member of the Centenary United Methodist Church. He lived his faith every day, and offered it to those in need. His home was a place of love, caring, and sharing. He was a wonderful father and devoted husband.

JAMES THORNTON PROCTOR, M.D.

James T. Proctor, M.D., Medical Director of the Child Guidance Clinic, died on February 4, 1984, after a brief illness at the age of 62.

Born in Blytheville, Arkansas, on November 20, 1922, he received his M.D. degree from the University of Kansas. He was serving as a Naval Officer on the U.S.S. Wright at the close of World War II. His residency in Psychiatry was completed at the U. S. Naval Hospital in Philadelphia, Pennsylvania.

Dr. Proctor had a strong interest in education (especially of medical professionals) throughout his career, with positions over the years as an Assistant Professor of Psychiatry at the University of North Carolina and Clinical Professor of Psychiatry at the University of Oklahoma. He was serving in that role for the Bowman Gray School of Medicine at the time of his death.

Dr. Proctor had a deep and abiding concern for children of all ages. He served as Medical Director of the Children's Medical Center in Tulsa, Oklahoma, prior to coming to Winston-Salem. He served in the role of Medical Director at the Child Guidance Clinic in Winston-Salem from 1973 until his death.

His wife, Bobbie Lee Hilton Proctor, died in 1968. Dr. Proctor is survived by two sons: Kirk and Mark Proctor, and by his parents, Cloud Colbert and Hattie M. Garrett Proctor of Overland Park, Kansas.

ROLETTA O. JOLLY-FRITZ, M.D.

Dr. Roletta O. Jolly-Fritz, physician and psychiatrist, age 87, died in Greensboro on August 30, 1984. Born in Marion County, Iowa, September 17, 1896, she grew up on her parents' farm with her three younger brothers. During her childhood she often accompanied her grandfather, Lafayette Jolly, M.D., on his house calls by horse-drawn buggy and decided she would be a physician.

She attended the State University of Iowa, receiving her B.A. in 1921, and her M.D. from the College of Medicine in 1923. After further study at Iowa Psychopathic Hospital, Dr. Jolly-Fritz received her license as a psychiatrist. She had a long medical career which included private practice, work at Central State Hospital in Nashville, Tenn., Allentown State Hospital in Pennsylvania, Osawatomie State Hospital in Kansas, the Central Nebraska Mental Hygiene Clinic in Hastings, and the Guilford County Mental Health Center in Greensboro and High Point, N.C. After her retirement from fulltime work in 1979, she continued as a consultant for Guilford County Mental Health Center and for the Mandala Center in Winston-Salem, N.C.

In addition to her professional life, Dr. Jolly-Fritz enjoyed many activities and travels worldwide. She was married in 1925 to Ralph A. Fritz, who preceded her in death by one year, after 58 years of marriage. Surviving are their three daughters, Mrs. Lolita Binford of Tampa, Fla., Mrs. Jolee Robinson of Westbury, N.Y., and Mrs. Marcia Hartman of Bethlehem, Pa.; one brother, Lorin Jolly of Pleasantville, Iowa; and seven grandchildren.

A scholarship fund has been set up in her memory to sponsor women medical students at the University of Iowa. Gifts can be made: University of Iowa Foundation, Roletta Jolly-Fritz, M.D. Scholarship Fund, Iowa City, Iowa 52242.

Study in Process

The Duke University Psychology Department is conducting a study of coping with rape. The research is aimed at understanding the response to rape over time and the relative effectiveness of various coping strategies. Women who have been victims of rape at any time in their lives are appropriate for this study. Participation involves filling out a confidential questionnaire. In exchange, participants will be offered free informational sessions on coping with rape, a free therapy group, a free support group for partners, and referral to individual therapy. All of these services are optional, and participation is strictly confidential. For more information or to receive a questionnaire, please call Dr. Susan Roth, 919/684-3645.

Names in the News

Dr. William L. Wood, a physician in Yadkinville, received the Distinguished Service Award during the North Carolina Public Health Association's 73rd annual meeting in Wilmington, NC. He received the award during the awards banquet on Thursday, September 20, 1984. The Distinguished Service Award is given each year to an

individual in recognition of outstanding contributions to public health in North Carolina over a period of years.

Dr. Wood serves Yadkin County Health Department as Medical Consultant. He has made many contributions to public health in Yadkin County by staffing mass immunizations, working in tuberculosis control and supporting the WIC (Women, Infants, and Children) Nutrition program and prenatal clinics.

As cited in his nomination, "the characteristic that above all others distinguishes Dr. Wood and marks him as a caring person," is his love of people. This sensitivity to the worth of every individual with whom he has contact underlies his entire career, and it was the strong motivation that led him into the study of medicine and a career in general practice.

Dr. Wood is married to Polly Hudspeth of Yadkinville. They have five children and eight grandchildren.

The Medical-Dental Staff at Forsyth Memorial Hospital has established an endowment in honor of the hospital's president who retired December 31, 1984 after 16 years as chief executive officer.

The **Harold G. Koach** Memorial Lectureship will attract nationally prominent speakers to the hospital each year to discuss problems facing physicians and administrators, as well as relations between the hospital and its medical staff.

At a banquet honoring Koach on October 26, the staff announced that $15,000 had been contributed to the endowment. Proceeds from the annual event will be used for the hospital as the medical staff designates.

For additional information, contact Bob Tannehill, Community Relations Director, 919/773-3402.

Letters to the Editor

Someone Loves Us

To the Editor:

There can be no better example of the change one person can effect than our *North Carolina Medical Journal*. It has now become one of the most welcomed publications coming across my desk. Many of my colleagues, I find, now share my enthusiasm. The articles are not only timely and topically interesting, but concise, well written, and most remarkably originate here in North Carolina. We are fortunate and grateful to share in your latest enterprise. Thank you.

H. Strawcutter, M.D.
101 West 27th Street
Lumberton 28358

Not Everyone Loves Us

To the Editor:

I tried but as usual failed to endure even the first paragraphs of two turgid articles in your most recent edition, and was about to file it under some banana peels in my Hefty kitchen-sized trash bag, when I noticed a fetching title: Goosey Patients, Relationship to Jumping Frenchmen, Myriachit, Latah, and Tic Convulsif (NCMJ 1984;45:556-558). The author of the article, E. Wayne Massey, successfully demonstrates two things: 1) All of these syndromes are pretty much alike, and 2) You can publish just about anything in the *North Carolina Medical Journal*.

Of particular (or should I say peculiar) interest, though, is the description, circa 1880, by Dr. George Beard, of the Jumping Frenchmen of Maine. French-Canadian they were, lumberjacks, living on Moosehead Lake in Maine. The doctor notes that if two of them were to stand toe to toe and be startled, they would "strike each other simultaneously with severe blows." (Massey's words) Then what happened?

Dr. Beard doesn't say. Not only does he discreetly neglect to tell the reader about the terrible brawl which must have ensued, he never explains how it is that a putatively compassionate man of the healing art could sneak up on a couple of Jumping Frenchmen in such an obviously precarious position and then scare the poor devils into fisticuffs.

As doctors, we must all bear his shame.

Robert Olds, M.D.
ECU School of Medicine
Greenville 27835

The Author Responds:

To the Editor:

Thank you for sharing Dr. Olds' letter with me. He read it, learned from it, had reactions to it, and took time to write the *North Carolina Medical Journal* a reply. I believe that would fulfill an educational process, the purpose of any journal, and my goal in writing.

E. Wayne Massey, M.D.
Duke University Medical Center
Durham 27710

Medical Mystery and the Whistle Blower: Several Responses to and from the Author

To the Editor:

The act of writing the article, as requested, for the *North Carolina Medical Journal* (October, pages 567-575) about my hospital experiences and chemotherapy gave me a great deal of pleasure. It served as a therapeutic release from side effects as well as a kindling of creative fires. It is nice to be back at my desk — this time with an Apple IIe. I would have hated to miss this high-class improvement over my old worn-out typewriter.

In addition, writing for the *Journal* gave me a feeling of honor. To be a published author in this superlative magazine, following articles by skilled physicians, just has to be a red-letter experience. Dr. Craige's lively cartoons added exactly the right note of humor (some of it wry) which helped me through so many of the tough days.

As if this were not enough, there have been numerous telephone calls as well as letters expressing appreciation for the article, some of them from cancer patients, others from relatives or friends of cancer patients. It is a great reward to know that any person, in reading the article, might find a degree of comfort or, perhaps, an affirmation of life beneath, beyond and even because of the ordeal.

With sincere thanks to all of you for giving me the opportunity to share my belief in faith and fun.

Mebane H. Burgwyn
Route 1, Box 424
Jackson 27845

"It was with great interest that I read your excellent article in the recent issue of the *N. C. Medical Journal* relating your experiences and health problems. I certainly commend you on your positive attitude toward your illness, and would have to think it played a great part in your recovery. Having experienced severe illness on several occasions in my life I feel in a position to sympathize with you in what you have experienced; and to rejoice with you in your recovery which I feel, like mine, was a work of the Lord along with that of the physicians."

Robert B. Outland, Sr., M.D.
Rich Square 27869

"It really helps to know someone else has experienced the same thing and come through so well. I am half way now and am looking forward to the final treatment, although I have had far fewer side effects than most. I understand about 'waiting.' Jim and I have about mastered

that skill for it is wait, wait and wait! I feel as you mentioned as I look around the waiting room. I feel far better than some and I am most thankful."

Helen Creech

"You have my highest admiration for your extraordinary courage and spirit — and the incredible fact that you kept your sense of humor throughout. I think it was wonderful that you wrote about your treatment and recovery; it will surely offer solace to many who are still suffering and inspiration to all who read it."

Grayce P. Northcross
3626 N. St., N.W.
Washington, DC 20007

Prescriptions

To the Editor:

We were very pleased to read Dr. John A. Ewing's article entitled "Physicians, Prescriptions and Prescription Drugs" in the *NCMJ* October issue (page 669-70). The Drug Enforcement Administration is, of course, quite concerned with the abuse of controlled pharmaceuticals. Time and again these substances surface in emergency room situations and overdose deaths. There can be no doubt that a vigilant, well educated medical community has a positive impact on drug diversion and drug abuse. We feel that Dr. Ewing's treatment of the issue was accurate and on target. Law enforcement efforts will only be successful when they are exercised in tandem with a proper respect for prescription drugs and a prudent attitude during the prescription process.

Thomas V. Cash
Special Agent-in-Charge
Drug Enforcement Administration
Atlanta, GA 30303

Synthroid

To the Editor:

The article "New Wine in Old Bottles" by Francis A. Neelon, which appeared in the June 1984 issue (*NCMJ* 45:398-9), contains several erroneous statements that may mislead your readers.

Dr. Neelon quotes me incorrectly when he states that Synthroid® tablets now contain more thyroxine than they previously did. While Synthroid tablets were reformulated in early 1982, the reformulation involved only inactive ingredients and tablet potency was not changed.

Secondly, radioimmune assay is not used to standardize tablet size. Indeed, this type of assay has never been found to be satisfactory for tablet potency assays. The currently approved USP assay methodology is high performance liquid chromatography. In the case of synthetic levothyroxine, HPLC gives the same value as the older iodine assay. (This is not the case with dessicated thryroid preparations.) Thus, the change in assay method has not led to a change in tablet potency.

Finally, Dr. Neelon states that his patient was taking 0.175 mg per day of levothyroxine. Synthroid tablets have never been manufactured in this size. The medical literature clearly documents that different levothyroxine preparations have differing bioavailabilities and, if Dr. Neelon's patient was getting her prescription filled with various brands, or with generic substitutes, this may account for her changing serum thyroxine level.

David L. Horwitz, M.D., Ph.D.
Medical Director, Travenol Laboratories
Deerfield, IL 60015

The author's response:

To the Editor:

Dr. Horwitz raises three points in reply to my brief report about the reformulation of Synthroid tablets:

1. He states that I was incorrect in inferring from his earlier letter to me that the new formulation of Synthroid tablets contains more thyroxine than did the previous preparation. His earlier letter mentioned only that the tablets were a "newly reformulated product" and did not claim then that the "reformulation involved only inactive ingredients." Despite Dr. Horwitz' assertion that "tablet potency was not changed," several investigators have found that earlier formulations of Synthroid tablets contained only about 80% of the stated thyroxine content[1-3] while the new preparation contains close to 100% of the stated content.[2-5] The reason for the discrepancy is uncertain. Whether Dr. Horwitz' "inactive ingredients" were more active than we suspect or whether some other explanation pertains, it seems clear to me and to others[3, 4] that Synthroid tablets are now more potent than they used to be. I continue to have to lower the dosage I have prescribed for my patients on Synthroid. Like Dr. Hamburger,[3] I wish the manufacturer has told us of the reformulation in advance.

2. I misspoke when I stated that a radioimmune assay was used to monitor tablet content of thyroxin — as Dr. Horwitz points out, an HPLC assay is used. Both are noble techniques, capable of precise and accurate results. I apologize for the error, but continue to applaud the use of better methods to monitor the drug manufacturing process.

3. Finally, Dr. Horwitz points out (correctly) that Synthroid tablets have never been made in a 0.175 mg size and infers (incorrectly) that my patient must have been using bastard forms of levothyroxine to account for the hyperthyroidism she developed on Synthroid. In fact, Synthroid *is* made in 0.15 and 0.025 mg sizes. My patient and I capitalized on the mathematical property of addition by having her take one tablet of each size daily to provide 0.175 mg/day. It was never an ideal solution because nobody likes taking two pills when one will do. That now seems to be a moot point. Since nowadays most of my patients seem to get thyrotoxic on 0.175 mg/day, I rarely have to prescribe the cumbersome two tablet regiments.

Francis A. Neelon, M.D.
Duke University Medical Center
Durham 27710

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2. Stoffer SS, Szpunar WE. Potency of levothyroxine products. JAMA 1984;25:635-6.
3. Hamburger JI. Thyroxine preparations (letter). Ann Int Med 1984;101:140-1.
4. Stoffer SS. Thyroxine preparations (letter). Ann Int Med 1984;101:140.
5. Potency of oral thyroxine preparations. Med Lett Drug Therap 1984;26:41.

Canker Sores

To the Editor:

This is in reference to the article on Canker Sores in the November 1984 (page 719) issue of *NCMJ*. I would appreciate it if Dr. Burton and associates could comment on two observations I have made on this problem.

First, I have found the most effective treatment is the use of the silver nitrate stick. The stick is dipped in water and then directly applied to the ulcer until it turns white. The patient then rinses his mouth with water.

Second, I have seen what might be considered an "epidemic" within a family. As one member gains relief another develops the ulcers. This would strongly indicate a viral etiology or perhaps all members are under the same elements of stress.

Stanley Grosshandler, M.D.
4905 Richland Drive
Raleigh 27612

The author's response:

To the Editor:

We would like to thank Dr. Grosshandler for his observations. Topical silver nitrate, which acts as a caustic, is certainly a therapeutic alternative worth mentioning. Unfortunately, many patients will provide the opportunity to experiment with many of the listed therapies in an attempt to control this miserable and often relapsing condition. We are unaware of careful prospective clinical trials that evaluate the merits of one treatment over the other and would expect that the process of trial and error will establish the best treatment for a given patient. Until the etiology is established, it is unlikely a specific treatment will be available.

Our personal bias is that virus is related to the pathophysiology of oral ulcers in some patients. The epidemic mentioned by Dr. Grosshandler is certainly compatible with that notion and also supports theories of a genetic predisposition. Clusters of cases provide an excellent opportunity to evaluate both possibilities.

Claude S. Burton, M.D.
Division of Dermatology
Duke University Medical Center
Durham 27710

Features for Patients

To the Editor:

For many months I have enjoyed the section in the *North Carolina Medical Journal* on patient information. It is written in a way that patients can quickly comprehend and get a lot out of.

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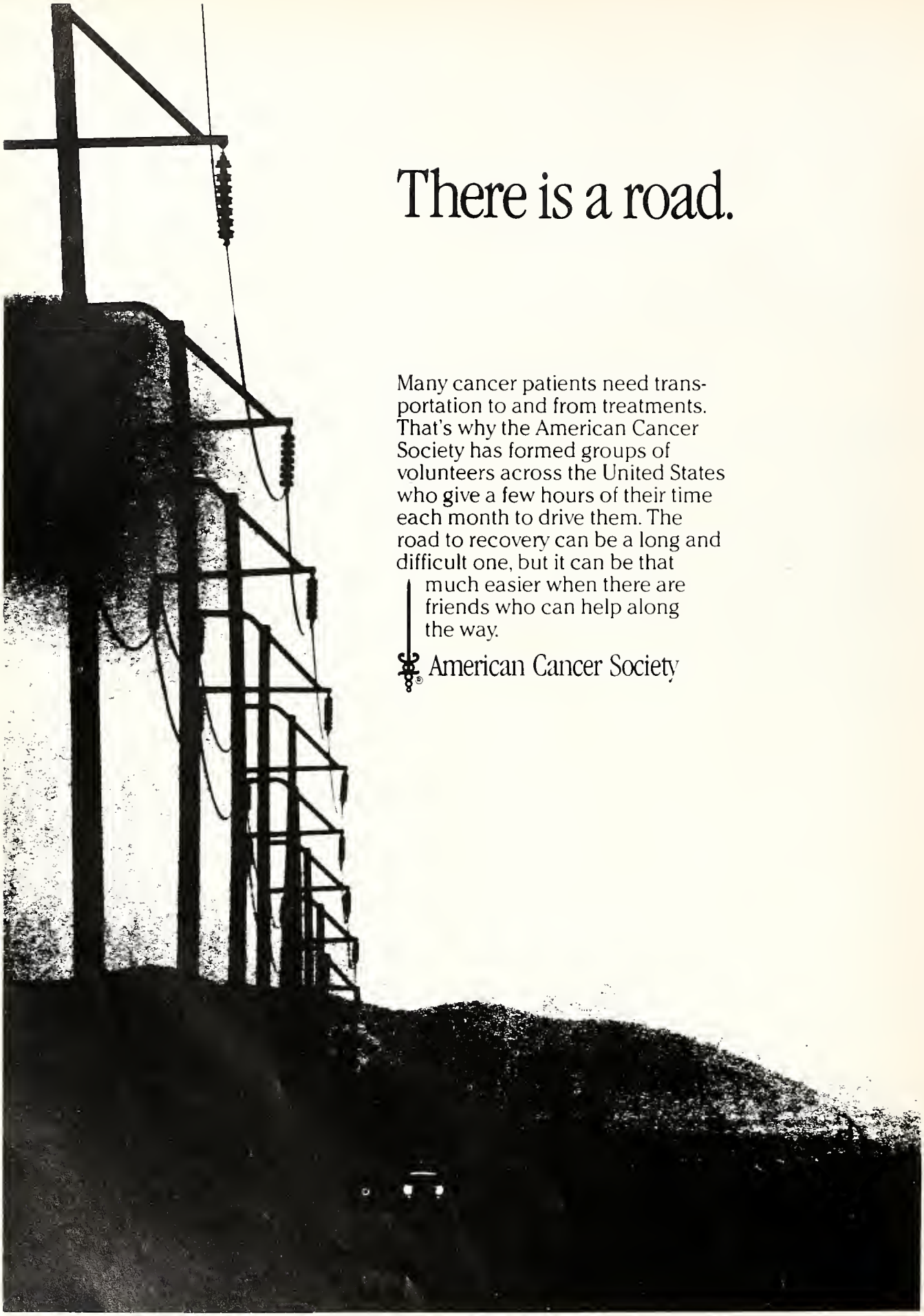
Keep up the excellent work.

C. R. Fernandez, M.D.
Medical Director
Nalle Clinic
Charlotte 28207

The Editor's Response

I appreciate your taking the time to write me about the patient section of the *Journal*. Reprints are not available but you are welcome to duplicate whatever you wish.

Eugene A. Stead, Jr. M.D.



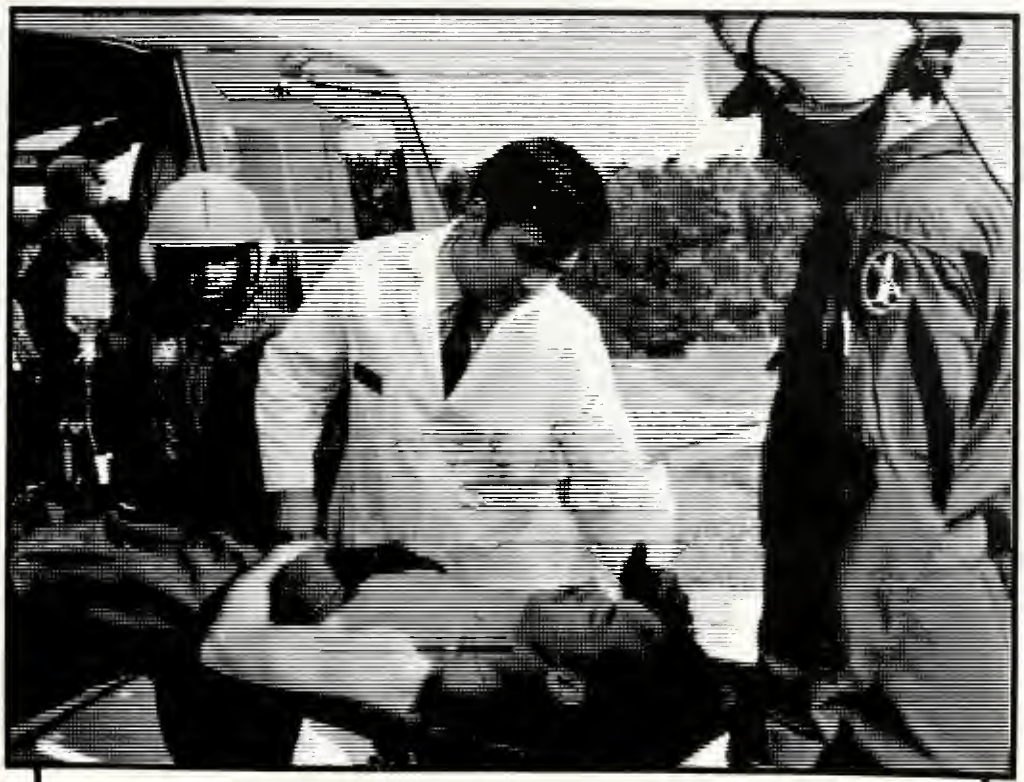
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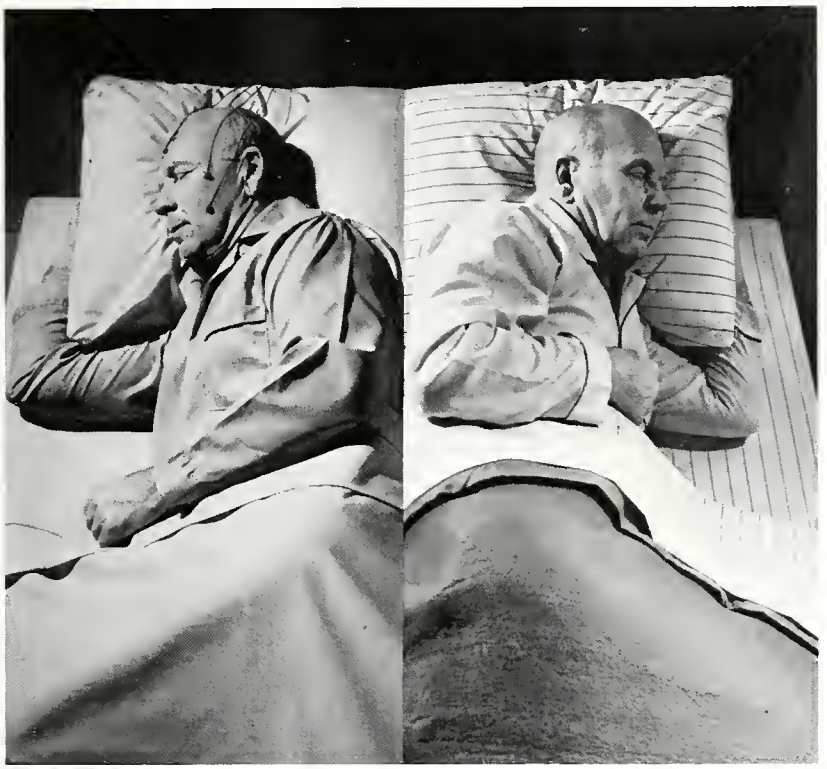
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References: **1.** Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res 9*(1):85-99, 1983. **10.** Monti JM: *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep 5*(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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ABOUT THE COVER: Dr. Allison of East Carolina University initiated the helicopter section for this month's issue when he sent me his paper. He was therefore offered the option of paying for the cost of having the ECU helicopter in color on the front cover. He declined. Duke accepted the opportunity and its helicopter is on the cover. [Photo by Anthony Benson, Division of Audiovisual Education, Duke Medical Center.]

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SCIENTIFIC ARTICLE

Maternal Mortality in North Carolina: A Historical Survey and Current Update

W. Joseph May, M.D. and Frank C. Greiss, Jr., M.D.

• *A five-year update (1976 to 1980) and review of maternal mortality in North Carolina based on 35 years of continuous analysis.*

THE Maternal Mortality Committee was constituted by the North Carolina State Medical Society in 1945. Three thousand seven hundred and eighty maternal deaths have been reviewed and analyzed through the Committee during the 35-year period. Eighty-five maternal deaths studied for five year analysis 1976 to 1980 are reported with a mortality rate of 23 per 100,000 live births. Two deaths complicated 127,332 abortions for a rate of 1.46 per 100,000. Direct and indirect causes of death for the periods 1946 to 1950 and 1976 to 1980 are compared. There has been a 90% reduction in maternal mortality in North Carolina during this 35-year period.

Historical Background

In the early 1940s, North Carolina was a predominantly rural state with a minimum of organized prenatal care. Medical specialists in Obstetrics and Gynecology were limited to the larger cities and the two four-year medical schools then extant. Each year approximately 100,000 live births occurred, two-thirds in the white race and one-third in the non-white races. Over 97% of white deliveries were attended by a physician with 20% occurring at home. While two-thirds of the black deliveries were attended by physicians, about two-thirds occurred at home and half of these were attended by untrained "granny" midwives. It is not surprising that North Carolina's maternal mortality ranked 37th in the United States.

It was on this background that in 1945, Dr. Oren Moore, then President of the North Carolina State Medical Society, constituted a new Maternal Welfare Committee whose initial charge was to study maternal mortality in the state. The prime mover of this idea, Dr. Frank R. Lock of Winston-Salem, who was to become the 14th President of the American College of Obstetricians and Gynecologists, was appointed Chairman of this Committee. Other members of the original Committee were prominent obstetricians-gynecologists from representative areas of the state and included Dr. Robert A. Ross of Durham, the 20th President of American College of Obstetricians and Gynecologists. In cooperation with the State Board of Health, the *modus operandi* of the Committee was to review anonymously case records of maternal deaths and to communicate their findings and suggestions for prevention to the involved physician. Thus, progress was to be by education rather than coercion, a process designed to encourage cooperation by attending physicians. In 1950, Dr. James F. Donnelly of Raleigh became Chairman of the Committee and in 1962 Dr. W. Joseph May replaced him and serves as the leader of the Maternal Mortality Study Project to the present.

From the Department of Obstetrics and Gynecology, Bowman Gray School of Medicine, Winston-Salem 27103.

Material and Methods

Through December 31, 1980, the records of 3,780 maternal deaths have been reviewed and analyzed. The classification of obstetric causes of death, which may be direct or indirect, recommended by the Committee on Maternal and Child Care of the Council on Medical Service, American Medical Association, is used. This defines a maternal death as "the death of any woman dying of any cause whatsoever while pregnant or within 90 days of the termination of the pregnancy, irrespective of the duration of the pregnancy at the time of termination or the method by which it was terminated."[1] A direct obstetric death is a death resulting from complications of the pregnancy itself, from intervention elected or required by the pregnancy, or resulting from the chain of events initiated by the complications or the intervention. An indirect obstetric death is a death resulting from disease before or developing during pregnancy (not a direct effect of the pregnancy) which was obviously aggravated by the physiological effects of the pregnancy and caused the death. With the cooperation of the North Carolina State Health Department, birth certificates have been cross-checked with death certificates to assure completeness of data collection. Since the advent of elective abortions which now comprise over 25% of conceptions in North Carolina, maternal mortality rates have been expressed as a function of both total live births and total conceptions (live births plus elective abortions). This permits more realistic comparisons with earlier data and with national data.

Results

During the first five years of the study, 1946-50, 532,310 live births and 914 maternal deaths occurred (172

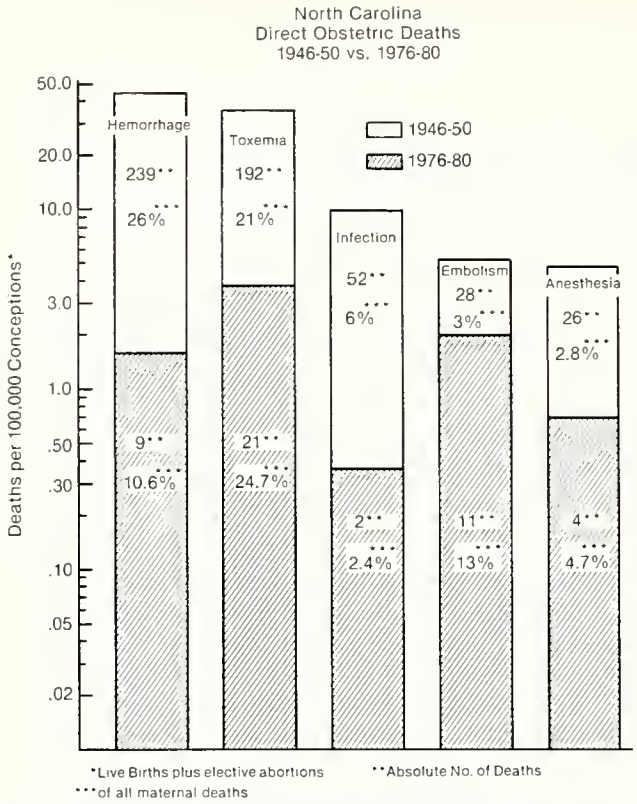


Figure 1. *Semi-log graph comparing distributions of maternal deaths by classification in North Carolina for the periods 1946-50 and 1976-80.*

per 100,000).[2] During the period 1976-80, 369,779 live births, 553,113 conceptions and 85 maternal deaths occurred (23 and 15 per 100,000, respectively). This represents a 90% reduction in maternal death rates during the 35 year period. Distribution of deaths by classification are compared for the two periods in figure 1. Relative to the 1946-50 period, the percentage of deaths from direct obstetric causes have decreased and those from indirect obstetric causes have increased. This distribution has been essentially the same since 1966.

Deaths by classification, major direct causes and race for 1976-80 are shown in table 1. The ratio of non-white to white maternal mortality rates has been surprisingly constant since 1966 varying between 2.62 and 2.72 during each five year period. However, this represents greater than a 50% reduction from the 6.0 ratio extant during the first half of the overall study period. Of the major direct obstetric causes of death, the ratio approaches parity only with vascular emboli (1.4 in 1971-75 and 1.70 in 1976-80).

During 1976-80, two deaths complicated 137,332 elective abortions for a rate of 1.46 per 100,000. The classical maternal mortality rate exclusive of elective abortions was 19.97 per 100,000 live births, 13.7 times greater. One woman died of an amniotic fluid embolism complicating a mid-trimester saline abortion and the other died of lidocaine toxicity during a suction curettage at 10 weeks gestation. The deaths of two additional women first encountered moribund or dead from septic abortions may have been prevented by legal elective abortions.

Direct obstetric causes of death for the periods 1946-50 and 1976-80 are compared in figure 2. Toxemia of pregnancy has been the leading individual cause of death for the past 15 years of the study. Relative to the overall reduction in direct obstetric deaths, those from vascular emboli have not kept pace reflecting most probably the less preventable nature of these complications.

Specific causes of death within generic causal groups for 1976-80 are shown in table 2. The following observations are noteworthy. One-third of the deaths from hemorrhage were from ectopic pregnancy. Two of these could have been prevented had today's rapid and highly sensitive tests for human chorionic gonadotropin been available. Overall

Table 1
Maternal Death Rates* by Race, Classification and Major Direct Causes, North Carolina, 1976-80

	Non-white	White	Non-white/ White
Direct Obstetric	15.8	4.9	3.23
Hemorrhage	3.8	0.5	7.60
Toxemia	6.5	2.4	2.70
Infection	1.6	0.0	—
Embolism	2.7	1.6	1.69
Anesthesia	1.6	0.3	5.30
Indirect Obstetric	6.5	3.0	2.17
Total Obstetric	26.2	10.0	2.62
Total Obstetric (1971-75)	75.0	27.6	2.72
Total Obstetric (1966-70)	116.9	43.9	2.66

* Deaths per 100,000 conceptions

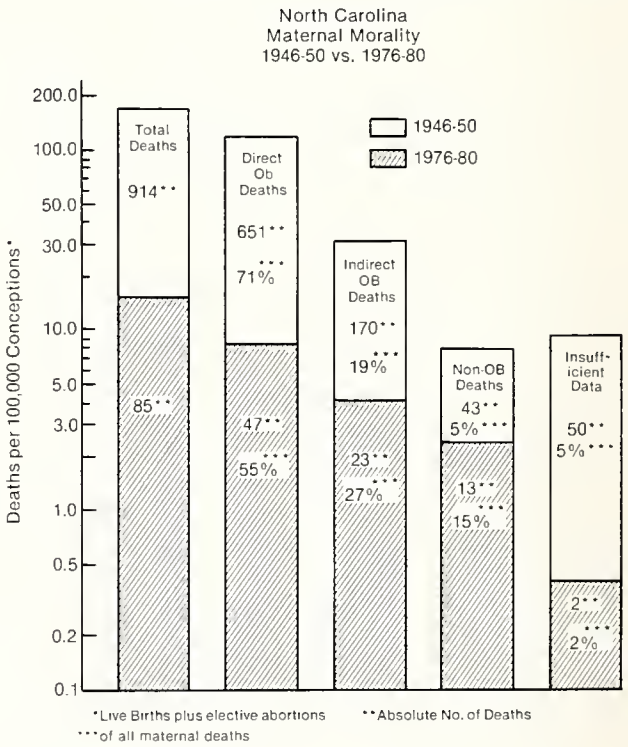


Figure 2. *Semi-log graph comparing major causes of direct obstetric maternal deaths in North Carolina for the periods 1946-50 and 1976-80.*

Table 2
Specific Causes of Maternal Deaths in North Carolina, 1976-80

	No.
Hemorrhage	
Ectopic pregnancy	3
Uterine perforation/rupture	2
Incomplete abortion	1
Placenta accreta	1
Abruptio placenta	1
Postop hemorrhage	1
Toxemia	
Cerebrovascular accident	7
Coma/convulsion	6
DIC/multiple organ failure	4
Renal failure	2
Heart failure	2
Infection	
Septic abortion	2
Embolism	
Blood clot	7
Amniotic fluid	3
Air	1
Anesthesia	
Aspiration	2
Local anesthetic toxicity	2

six of the nine deaths were considered medically preventable. Had the other three patients sought medical care, they too would not have died.

In addition to the classical causes of death from toxemia, disseminated intravascular coagulopathies associated with multiple organ failure have emerged as a significant factor. Usually these women, although seriously ill, were thought stable when without premonitory signs they began a rather sudden inexorable downhill course.

Aspiration of gastric contents continues to be an ever present potential cause of anesthetic deaths in nonpregnant women accounting for 50% of anesthetic deaths in this series.

Indirect obstetric deaths for the two study periods are compared in figure 3. Cardiac disease continues to be the single largest cause of death in this classification. With the exception of three deaths from sickle cell disease, the remaining deaths were from individual rare medical conditions.

Discussion

Those physicians who have participated in North Carolina's maternal mortality study can consider their efforts a factor in the steady decline in mortality rates (figure 4). The obvious medical progress over the past three decades, along with economic and social forces have had major impact on improved health care in general. The increased affluence and education of North Carolina's populace, more rapid transportation and racial integration have increased the desire for and improved access to quality medical care. In particular, legalization of the elective abortion significantly accelerated the decline in maternal mortality rates. This is evident in figures 4 and 5 during the periods 1971-75 and 1976-80, particularly in the curve of deaths from infection.[3, 4] Since 1972, no deaths have been

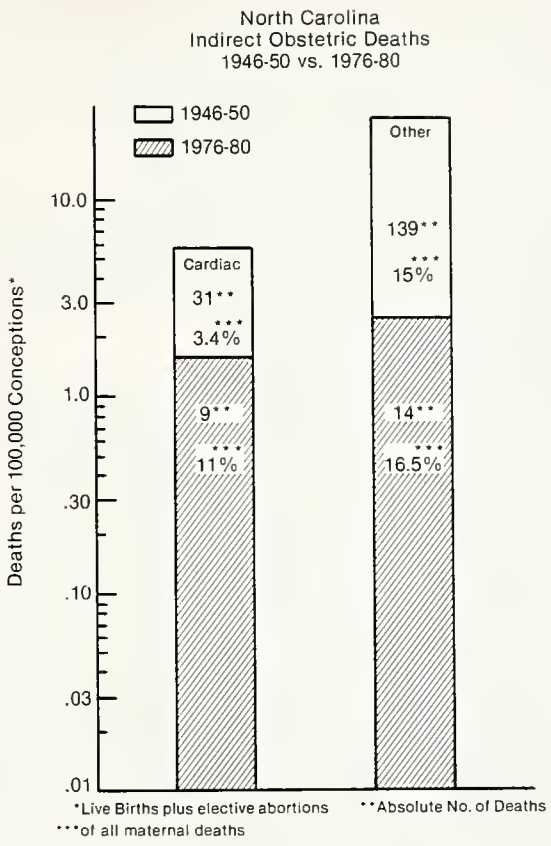


Figure 3. *Semi-log graph comparing causes of indirect obstetric maternal deaths in North Carolina for the periods 1946-50 and 1976-80.*

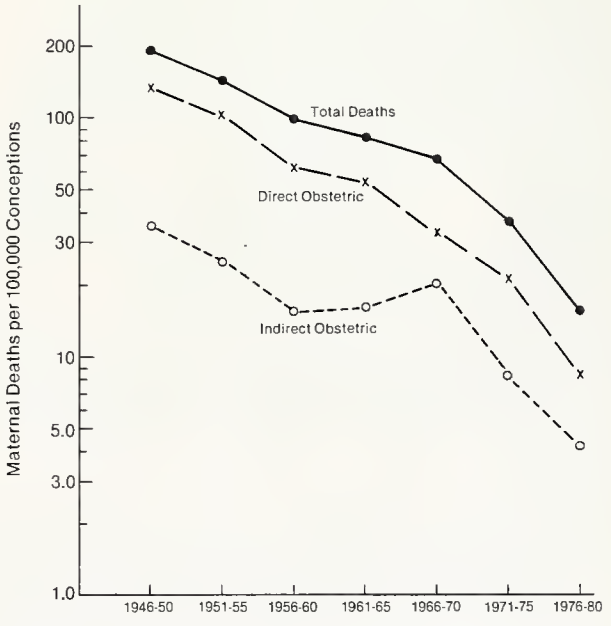


Figure 4. *Semi-log graph of maternal death rates in North Carolina according to major classification from 1946 to 1980 by 5 year cohorts.*

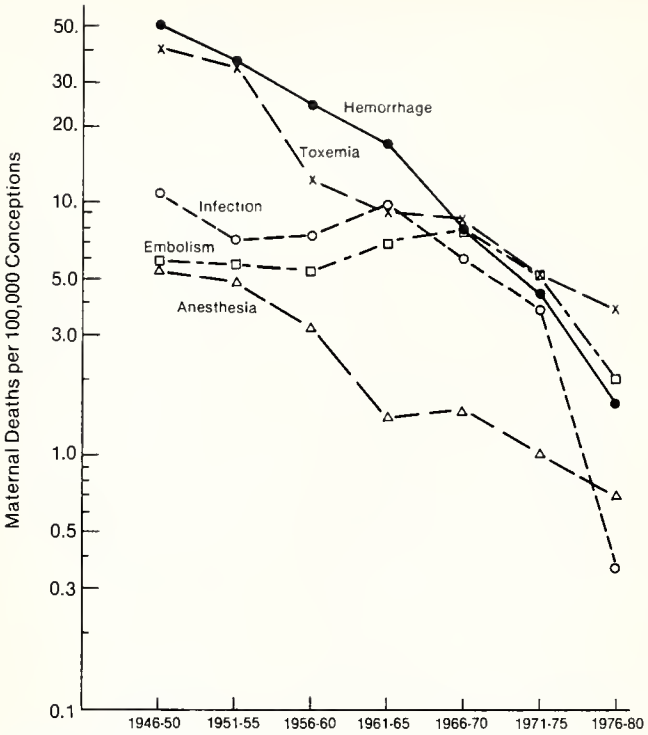


Figure 5. *Semi-log graph of major direct obstetric death rates in North Carolina from 1946 to 1980 by 5 year cohorts.*

attributable to criminal abortions although two deaths in the 1976-80 data are suspect. This is in contrast to eight deaths from criminal abortion during 1971 and 1972, the years immediately preceding the Supreme Court decision legalizing elective abortion.

North Carolina's progress in reducing maternal mortality parallels that of the United States as a whole and that of the South Atlantic region. For the year 1979,[5] North Carolina's maternal mortality ranked 32nd in the nation, changed relatively little from 1945. However, a closer look at these statistics indicates clearly that it is the non-white races that remain at highest risk for maternal mortality. For example, the non-white to white maternal mortality ratios for total deaths were 3.54 nationally and 2.62 for North Carolina. Similar ratios for direct obstetric deaths were 3.17 nationally and 3.23 for North Carolina. These data indicate that future efforts to reduce maternal mortality must focus upon improved education and availability of prenatal care for the non-white races.

Despite the original design of the North Carolina study, it met resistance by some physicians so that during the early phases of the study, paucity of data frequently precluded precise categorization. This resistance gradually diminished but during the past 10 years, the increasingly litigious nature of our society has made many physicians reluctant to make records of such deaths available. The continued support of the North Carolina State Medical Society and interested physicians throughout the state and the maintenance of strict anonymity has allowed accurate data collection. The fact that 65% of patients in the 1976-80 period were autopsied has been of significant value also. However, in today's climate of quality assurance, physicians must become increasingly aggressive in their efforts to further diminish preventable deaths in this very sensitive area. Although the very low maternal mortality rates currently extant and potential legal implications promote little enthusiasm for maternal mortality studies, it is clear that even lower rates are attainable and that new causes of death must be guarded against. For example, at least 20 of the 48 direct obstetric deaths currently reported were preventable, accountability equally distributed between physicians and patients. In addition, today's high technology raises the specter that iatrogenic deaths may be on the rise. This is especially true in the areas of invasive techniques for cardiovascular monitoring and the use of potent beta agonist drugs for inhibiting labor.

The medical profession is becoming more and more accountable for its activities. Under these circumstances, it becomes vital that continued reappraisals of morbidity and mortality statistics are made so that we, the practicing physicians, may remain the determiners of standards of excellence in medical care.

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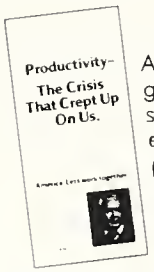
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SCIENTIFIC ARTICLE

The Proper Use of Systemic Fluoride Supplements with Children in Medical and Dental Practices

Steven M. Levy, D.D.S., James W. Bawden, D.D.S. and Ronald H. Levine, M.D.

• *Because children usually do not visit a dentist until age 3 or 4, the physician needs to see that they are introduced to fluoride in proper doses and by appropriate routes as early as possible.*

Introduction

The appropriate use of fluoride remains the best defense against dental caries. This is true despite extensive efforts to develop improved methods of mechanical plaque removal, to develop chemical agents that safely and effectively reduce the cariogenic activity of bacteria, and to reduce the frequency of intake of cariogenic foods by modifying dietary practices.[1] Occlusal sealants are an important new weapon in caries control, but their effectiveness depends heavily on the ability of fluorides to control smooth surface caries. Although the mechanisms by which fluorides exert their caries-inhibiting effects are not fully understood, they are still thought to be:

(1) reduction of enamel solubility;
(2) remineralization of early carious lesions; and
(3) action on plaque bacteria.[2]

There has been greater interest in and understanding of the remineralization process in recent years, showing that many early carious lesions may be reversible if treated promptly and properly with fluoride.

Fluoride products are intended for use either systemically or topically. After the ingestion of systemic fluorides, fluoride is incorporated into the developing tooth structure. In contrast, topical fluorides only work locally on the superficial layers of enamel and on plaque. Methods of delivering systemic fluorides in the United States include community water fluoridation, school water fluoridation, and dietary fluoride supplements. Topical fluorides may be applied professionally or self-applied. They include fluoride solutions and gels (applied in trays or with a toothbrush or applicator), fluoride dentrifices (toothpastes), and fluoride mouthrinses. Also, topical benefits result from drinking fluoridated water or from chewing fluoride tablets. A comprehensive fluoride program may include a systemic form and several topical forms. The systemic and topical modes should not be used in lieu of each other, but should complement each other.

There are many good discussions of these methods of delivering fluorides, including those by Horowitz,[1] Bawden and Stanmeyer,[2] and in the American Dental Association's *Accepted Dental Therapeutics*.[3] Bawden has also written an article detailing a scientific approach to the practitioner's use of topical fluoride products.[4] These references should be consulted for further information.

The purposes of this paper are to explain the need for, and the importance of, systemic fluoride supplements in North Carolina, and to review the proper protocol for supplement use. The article should be helpful to physicians in providing optimum preventive care for young patients.

The Need for Systemic Supplements

Community water fluoridation is recognized as the most efficient and cost-effective method of providing the recommended levels of systemic fluoride for the prevention of dental caries.[5, 6] Unfortunately, approximately one-half of the population of North Carolina (and the United States) drinks water that is not optimally fluoridated.[7] In North Carolina, 84% of the population served by community water systems is receiving fluoridated water (unpublished observation). However, because the state has such an extensive rural population, this figure represents only 49% of North Carolina's total population. In fact, if *all* community water systems were fluoridated, 40% of the state's population would remain without access to fluoridated water.

Alternative sources of systemic fluoride are necessary if more of our children are to be provided the caries preventive benefits of systemic fluoride. North Carolina has been a pioneer in school water fluoridation and it leads the nation in the number of installations. There are presently 133 school fluoridators operating in North Carolina, serving some 52,000 children (unpublished observation). Generally, the water from these fluoridators contains 4.5 parts-per-million (ppm) of fluoride to approximate the fluoride intake that would take place if the children were drinking water fluoridated at the optimal 1.0 ppm all day, every day. The

From The Department of Human Resources, Raleigh 27602, and The School of Dentistry, The University of North Carolina, Chapel Hill 27514.

students drink the school water only 6-7 hours daily for approximately 180 days per year. Children drinking school water flouridated at 4.5 ppm will experience substantial caries reductions (~40%), particularly in the late forming teeth.[8]

Children drinking water from a fluoridated community system or a school fluoridation system *should not receive fluoride supplements*. Further information about community and school water fluoridation in your area may be obtained from your local dental public health personnel or from the North Carolina Dental Health Section: 919/733-3853. The Dental Health Section also can provide lists of communities and schools in North Carolina that are optimally fluoridated.

Fluoride Supplement Use

For those children who do not drink fluoridated water either at home or from a school fluoridator, the use of systemic fluoride supplements in tablet or drop form is a safe and effective means of reducing the incidence of dental caries.[9-15] In order to receive maximum preventive benefits, we feel that the supplements must be taken daily from birth until age 13.

Several studies have investigated the extent to which fluoride supplements have been used in the United States. National surveys conducted in 1975 and 1982 by the American Dental Association (ADA) revealed that 53% and 60%, respectively, of general practicing dentists prescribed fluoride supplements.[16, 17] In 1978, Margolis and coworkers found that 81% of pediatricians and 63% of family practitioners who responded to their survey prescribed supplements.[18] In a fluoride-deficient area in Texas, 35% of responding physicians reported that they routinely prescribed supplements.[19] The ADA found in 1982 that 79% of responding physicians prescribed fluoride supplements.[17] The results from a recently completed 1984 survey of dentists in North Carolina showed that 78% of general practicing dentists statewide were prescribing fluoride supplements (unpublished observation). These studies have also shown that many providers are not aware of the proper dosage guidelines, the contraindications (e.g., fluoridated water), and the actual fluoride concentrations in the area's water supplies. This is true among both those prescribing supplements and those not prescribing.

The next sections will review in detail the proper protocol for determining whether supplementation is indicated and, if so, the correct supplement dosage to be prescribed.

Supplement Protocol

It is important for children to receive the *appropriate total dose* of fluoride. This can be accomplished only if the physician knows the fluoride levels of the patient's home and other water supplies (e.g., school, day care, etc.). Fluoride levels exceeding the optimal are associated with an increased risk of dental fluorosis (mottling). Although dental fluorosis is primarily an aesthetic concern, moderate to severe cases often involve pitting and other defects of the tooth surface. Therefore, to avoid overdosing, the physician should know which communities and schools in the area are fluoridated and the levels of fluoride concentration (i.e., 1 ppm versus 4.5 ppm).

A separate water sample should be submitted to the N.C. State Laboratory of Public Health in order to determine the fluoride content of each community, school, or individual water supply if the physician does not have *prior specific knowledge* of the level. Because there can be significant fluctuations in well water fluoride content, even in a small geographic area, one *should not* rely on the results of a sample from a different water source, no matter how near.

Water Sampling Procedures[20]

The North Carolina State Laboratory of Public Health will analyze individual patients' water samples for health professionals. The procedure for ordering sample bottles is as follows:

1. Call or write the Laboratory of Public Health specifying the number of fluoride sample bottles required. Address: State Laboratory of Public Health, Division of Health Services, P. O. Box 28047, Raleigh 27611-8047. 919/733-7308.

2. The laboratory will mail you the bottles and report forms. There will be a fee of 50 cents per bottle plus shipping charges; the patient should provide return postage. (The cost is significantly less than the actual cost of the analysis. Similar programs in other states generally charge $2.50-$5.00 per sample.[21-23])

3. In consultation with the parent, the physician or a member of his/her staff should fill in all of the requested information on the report form except the name of the person who subsequently collects the sample and the time when that occurs. The bottle, the form, and the return address label should be placed in the container and given to the parent to take home (or to school, etc.) to collect the sample. The tap should be run for 30 seconds, the bottle nearly filled and firmly stoppered, the address label attached, and the sample mailed.

4. The results will be sent to the health professional indicated on the report form within a week or two after the sample is mailed.

Frequency and Results of Water Sample Analyses

A recent study investigated the frequency, distribution and results of analyses for fluoride content of drinking water samples in North Carolina.[24, 25] There were 1,935 water samples submitted to the State Laboratory of Public Health by North Carolina health professionals between December 1, 1982 and May 31, 1983. Copies of these reports are kept on file by the Dental Health Section which also monitors community and school fluoridation. Table 1 shows the distribution by provider type. Practicing dentists submitted 39% of these samples, 35% were mailed in by physicians, 22% by health department personnel, and 5% of the providers could not be classified.

Table 2 shows that, in comparison with the total numbers of providers practicing in the state, only 8% of the dentists and 3% of the physicians most likely to provide diagnostic and preventive services to children submitted water samples.

Because of the largely rural nature of North Carolina, many providers in fluoridated communities treat patients who reside in nearby nonfluoridated areas. Therefore, most providers treating young children should have occasion to

Table 1
Distribution of Water Samples by Provider Type[24, 25]

Provider	Number	Percentage
Dentists	746	38.5
Physicians	671	34.7
Health Depts.	423	21.9
Unknown	95	4.9
Total	1,935	100.0

Table 2
North Carolina Health Professionals Requesting Water Analysis[24, 25]

Health Group	Number Sampling Water	Number Practicing[26]	Percent Sampling Water
Dentists	156	1984*	8
M.D.s	61	1983*	3
Health Depts.	20	83	24

* Only those most likely to be routinely providing diagnostic and preventive services to children are included. Dentists included are those in general practice and pedodontics and students in dental school. Physicians are in general practice, family practice, and pediatrics. It was not possible to determine how many of these actually treat children. Therefore, these figures are likely overestimates.

Table 3
Supplemental Fluoride Dosage Schedule* (in mg. of fluoride per day)

Age of Child	Parts per Million Fluoride in Water Supply < 0.3	0.3 to 0.7	> 0.7
Birth to 2 yrs.	0.25	0	0
2-3 yrs.	0.50	0.25	0
3-13 yrs.†	1.00	0.50	0

* Recommended by the Council on Dental Therapeutics of the American Dental Association, by the Committee on Nutrition of the American Academy of Pediatrics, and by the American Academy of Pediatric Dentistry.
† The American Academy of Pediatrics recommends providing tablets through at least age 16.

Table 4
Frequency of Various Fluoride Levels in North Carolina Water Samples[24, 25]

Fluoride (ppm)	Frequency (%)	Supplementation Recommendations*
< 0.3	87	Full
0.3-0.7	6	Reduced
> 0.7	6	None

Note: Fluoride levels greater than 2.0 ppm were found in 1% of the samples.
* See table 3.

assay water for fluoride content on behalf of their patients and prescribe fluoride supplements. Since many more births occurred in nonfluoridated areas than there were samples submitted,[27, 28] either (1) many children in need are not benefiting from fluoride supplements and/or (2) many receive supplements without proper water fluoride assay. Of those samples submitted by dentists, 29 pedodontists provided 44% and one pre-paid dental plan clinic sent in 29%. Thus, a small number of dentists requested most of the assays. A small number of physicians and health departments similarly provided the majority of samples from these sources. Eight physicians submitted 71% of the physicians' total number of samples, and 5 of the 83 health departments submitted 78% of the samples from these departments. Samples were received from 76 of North Carolina's 100 counties, but 53% came from only 9 counties. Clearly, a small number of practitioners in each provider category requested fluoride analyses.

The present guidelines for systemic fluoride supplements recommended by the American Dental Association, the American Academy of Pediatric Dentistry, and the American Academy of Pediatrics are seen in table 3.

The revised pediatric guidelines are now identical to the ADA recommendations except for the age at which supplements may be discontinued.[29, 30] In the past, the different dosage schedules had caused problems because physicians and dentists were not following the same schedule.

As seen in table 3, any water fluoride level greater than 0.3 ppm requires adjustment from the full dosage supplement.

Table 4 shows that 12% of the study samples warranted adjustment.[24, 25] One percent of the samples had fluoride levels exceeding present EPA recommended guidelines for maximum contaminant level, more than twice the optimum level of 1.0 ppm. [To encourage and standardize proper fluoride prescription procedures, the North Carolina Dental Health Section has designated 1.0 ppm the optimal level for all of North Carolina, despite regional temperature differences which would otherwise require minor variations in the optimal level. This designated level of 1.0 ppm is well within the optimal range for all of North Carolina.] Of the 76 counties with at least one sample submitted, 8 counties (11%) had a reading greater than 2.0 ppm, 33 counties (43%) greater than 0.7 ppm, and 47 counties (62%) greater than 0.3 ppm.

Levels of fluoride requiring adjustment or withholding of supplement dosage were found in varied regions of the state, not just in the known belt of natural fluoride that runs through eastern North Carolina, South Carolina, and Virginia. Thus, it is necessary to sample the water supply before prescribing a fluoride supplement — unless the provider has *specific prior knowledge* of the fluoride content of the patient's water.

Determination of Appropriate Dosage

After determining the fluoride levels of a patient's multiple sources of water (either by submitting samples or obtaining information from water companies, schools, Dental Health Section, etc.), the physician must determine the supplement dose to prescribe. This is done after estimating the percentage of daily water intake from each source and consulting table 3. For instance, if a 3-year-old child consumes well water at home with <0.1 ppm fluoride, but goes to day school in down where the water is fluoridated at 1 ppm fluoride, one must estimate the water consumption from each source. If it appears that the child

consumes about half his water from each source, the net result would be the same as if the child were drinking water containing 0.5 ppm. One should then refer to table 3 to determine the correct dose (0.5 mg/day). A variety of similar circumstances can occur.

It is essential to determine whether an infant is being exclusively breast-fed, bottle-fed, or obtaining nutrition from both sources. Breast-fed babies should be supplemented fully, since there are very low amounts of fluoride found in human milk, even when the mother resides in a fluoridated area.[31] The major manufacturers of infant formulas have removed fluoride from their products which previously contained variable levels. An infant on formula now receives fluoride almost exclusively from the water that is mixed with the formula. The physician must determine the proportion of bottle-feeding and reduce the supplement accordingly for those infants receiving nutrition from both sources.

For purposes of fluoride intake calculations, an adult is assumed to consume daily an average of one liter of water. If the water is fluoridated at 1.0 ppm, then 1 mg of fluoride is consumed. An infant, then, according to table 3, should have a daily intake of about 0.25 liters of fluoridated water, or 0.25 mg of fluoride. The determination of fluoride intake can be difficult. The total amount of water consumed daily must be determined, whether it is in the water, in juice made from concentrate, formula from a concentrated powder or liquid, or in other forms. It should be recommended that parents try to standardize the amount of water consumed by the infant, as well as the type of formula (i.e., powder, concentrated liquid, etc.).

Since excessive fluoride can cause fluorosis, parents should contact the physician when changes occur in the infant's consumption of liquids so the fluoride supplementation can be adjusted. In a fluoridated community, a 1-year-old child drinking four 8-ounce bottles of formula daily would receive 1 mg of fluoride (four times the optimal) if concentrated powder were used, and 0.5 mg of fluoride (twice the optimal) if concentrated liquid (diluted 1:1 with water) were used. Using "ready to use" formula would mean that no fluoride is consumed via the formula, and the water or the supplement used should provide the infant's needed fluoride in the recommended amount. The practitioner must have a thorough understanding of the patient's total flouride exposure. Since most young children do not see a dentist before age 3 or 4, the complexities of controlling fluoride dosage for infants are largely the responsibility of physicians.

Fluoride tablets are now available in 0.25, 0.5 and 1.0 mg fluoride formulations. There are several commercial brands available.[3] Additionally, many pharmacies can provide a generic product. The tablet should be chewed before swallowing to provide topical benefit. Fluoride drops, providing 0.125 mg of fluoride per drop, should be used for those who cannot chew a tablet. No more than 264 mg NaF, or 120 mg fluoride, should be prescribed at one time for safety reasons.[3] The product should be kept in a "child-proof" container in a secure place. The biggest difficulty with fluoride supplements is patient compliance.[12-15, 32] The physician must routinely encourage and attempt to monitor the child's supplement use.

Conclusion

It is hoped that this article will encourage and assist physicians in North Carolina in providing the appropriate dosage of fluoride supplements to those children in need. The medical profession must work closely with dentists and other health professionals if systemic fluorides are to be used to greatest benefit in our population.

Summary[22]

1. All children should receive some form of systemic fluoride and appropriate forms of topical fluoride.
2. If a child is not receiving optimal home (1 ppm) or school (4.5 ppm) water fluoridation, then the physician should consider prescribing systemic sodium fluoride supplements (tablets or drops).
3. The correct dose must be determined based on patient age and fluoride content of the patient's multiple water sources.
4. Special attention is necessary concerning fluoride intake for children breast-feeding or consuming infant formula.
5. To arrive at the correct fluoride dose, these steps should be followed:
   A. *Always* have a sample of the home water supply analyzed for the fluoride content before prescribing a fluoride supplement. If the child drinks significant amounts of water from more than one source of unknown fluoride content, the other sources should be analyzed as well. The State Laboratory of Public Health will provide sample bottles, 919/733-7308.
   B. When the fluoride content of the water has been determined, the value and the child's age should be matched on table 3 to arrive at the correct supplement dose.
   C. If the child is drinking water from more than one source that contain various amounts of fluoride, one must estimate the percentage of the daily water intake from each source and adjust the dose accordingly. It is important to **thoroughly understand** the child's systemic fluoride exposure and to use sound judgment in calculating the dose.
   D. Over 130 schools in North Carolina have school fluoridators which fluoridate the water at 4.5 ppm. **Children who attend such schools should not receive a systemic supplement, even though their home water contains no fluoride.** Information on the schools in your area that have school fluoridators can be obtained from the county health department or the Dental Health Section in Raleigh at 919/733-3853.
6. The Dental Health Section can provide lists of communities and schools in North Carolina that are optimally fluoridated.

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days at a time. Due to package insert warnings for valproic acid, the patient on two occasions had valproic and doxepin levels determined plus PPT, Protime, LDH, SGOT, and SGPT. All were at desired levels.

Five months from her initial visit the patient was seen with plans to reduce her medications. During the course of the visit she remarked that she had experienced some abdominal distress the past several days. An examination of the abdomen was suspicious of an abdominal catastrophe and surgical consultation was immediately obtained. A diagnosis of ruptured diverticula was made and a colon resection was performed, resulting in a 17-day hospitalization. The patient made an excellent recovery.

The patient was not seen for three months during which period she had discontinued her medications as a result of her surgery. The facial pain had returned but not to the same degree as previously. The medication routine was restarted and she had immediate pain relief. Within a two-month period both doxepin and valproic acid had been discontinued with only occasional use of the diflunisal.

This lady represents the typical postherpetic neuralgia patient. In an effort to obtain pain relief she had consulted many physicians, receiving multiple prescriptions. She was indeed fortunate she had not become an iatrogenic drug abuser.

She manifested many signs of the chronic pain patient, including a reactive depression. This is found in as high as 80-90% of chronic pain problems.[4] Though her Zung index was only 33, the symptoms of sleep difficulty, loss of energy, admission of feeling depressed and crying clearly indicated she would benefit from a tricyclic antidepressant (TCA).

Amitriptyline and doxepin are the TCAs of choice in chronic pain,[5] with doxepin appearing to have the lesser incidence of side effects. It is postulated that the antidepressant blocks the reuptake of serotonin by the nerve endings and thus increases the concentration of serotonin at the receptor sites. This is clinically manifested by improved sleep, improved energy, decreased depression, and decreased awareness of pain.

A nonsteroidal anti-inflammatory (NSAID) was chosen for its non-addicting analgesic effect plus antiprostaglandin synthesis action.[6] The NSAID chosen has a twice-a-day dosage, making for better compliance, and it appears to have the least gastric irritation of commonly used NSAIDs. The patient was also advised to take the medication with food.

The anticonvulsants phenytoin and carbamizide have long been efficacious in the treatment of trigeminal neuralgia; however, in this case they had not been helpful, and therefore valproic acid was used.[7] The mechanism of action of this class of drugs in this problem is stated to be a reduction of post-tetanic synaptic transmission within the spinal cord, reducing the perceived sensation of pain.[2]

Of significant importance in the therapeutic success of this patient is her basic personality structure. A well-educated person, harboring no desire of secondary gain, her intense determination to defeat her medical problem and continue with her career played a major factor in her treatment.

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

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Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

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In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

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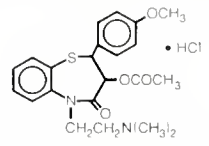
PROFESSIONAL USE INFORMATION

cardizem® (diltiazem HCl)

30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash asthenia (1.2%), AV block (1.1%). In addition, the following were reported infrequently (less than 1%) with the order of p tion corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, b dia, palpitations, congestive heart syncope.
Nervous System:	Paresthesia, nervousness, somn tremor, insomnia, hallucinations, and a
Gastrointestinal:	Constipation, dyspepsia, diarrhea, v mild elevations of alkaline phosphatas SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photose
Other	Polyuria, nocturia

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing epis vasospastic angina developed periods of transient asym asystole approximately five hours after receiving a single dose of CARDIZEM.

The following postmarketing events have been reporte quently in patients receiving CARDIZEM: erythema multifor kopenia; and extreme elevations of alkaline phosphatase SGPT, LDH, and CPK. However, a definitive cause and effect these events and CARDIZEM therapy is yet to be establish

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been Single oral doses of 300 mg of CARDIZEM have been well t by healthy volunteers. In the event of overdosage or exag response, appropriate supportive measures should be emp addition to gastric lavage. The following measures may be cor

Bradycardia	Administer atropine (0.60 to 1.0 mg) is no response to vagal blockade, ad isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fix degree AV block should be treated v diac pacing.
Cardiac Failure	Administer inotropic agents (isopro dopamine, or dobutamine) and diureti
Hypotension	Vasopressors (eg, dopamine or leva bitartrate).

Actual treatment and dosage should depend on the sever clinical situation and the judgment and experience of the physician.

The oral/LD_{50}'s in mice and rats range from 415 to 74 and from 560 to 810 mg/kg, respectively. The intravenous these species were 60 and 38 mg/kg, respectively. The ora dogs is considered to be in excess of 50 mg/kg, while leth seen in monkeys at 360 mg/kg. The toxic dose in man is no but blood levels in excess of 800 ng/ml have not been as with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerot nary Artery Disease or Angina Pectoris at Rest Due nary Artery Spasm. Dosage must be adjusted to each needs. Starting with 30 mg four times daily, before meal bedtime, dosage should be increased gradually (given in doses three or four times daily) at one- to two-day interv optimum response is obtained. Although individual patie respond to any dosage level, the average optimum dosa appears to be 180 to 240 mg/day. There are no available data ing dosage requirements in patients with impaired renal o function. If the drug must be used in such patients, titration s carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abo anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may b coadministered with short- and long-acting nitrates, have been no controlled studies to evaluate the an effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 1 0088-1771-47) and in Unit Dose Identification Paks of 1 0088-1771-49). Each green tablet is engraved with MARIO side and 1771 engraved on the other. CARDIZEM 60-m tablets are supplied in bottles of 100 (NDC 0088-1772-47) a Dose Identification Paks of 100 (NDC 0088-1772-49). Ea tablet is engraved with MARION on one side and 1772 on t

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SPECIAL ARTICLE

How Can We Know When We Are Doing More Good Than Harm For A Terminally-ill Cancer Patient?

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• *The suffering of terminally-ill cancer patients cannot be relieved if the physician is working with inaccurate information.*

THIS paper is about our attempts to relieve patients' suffering when death is inevitable and relatively imminent. An example of that situation is the care of terminally ill cancer patients.

My thesis is that sometimes we make inappropriate decisions toward our goal of relieving suffering in part because we are working with inaccurate information. Our eyes, ears, hands and minds have failed to provide us with an accurate view of the world as our patients see it. If this occurs, we (and more to the point, our patients) are doomed to failure even before we begin to make what might be regarded as clinical or ethical decisions.

The subject, then, is bias (a systematic error) in our perception of our patients, and its consequences. I will illustrate the failures attendant upon biased observation by anecdotes and by more formal science, original research.

Relieving Suffering and Preventing Untimely Death

First, let us consider our objectives for patients. I was taught as a medical student that our role as physicians is to relieve suffering and prevent untimely death. But not uncommonly one must choose between the two in an individual patient; that is, one might relieve suffering *or* prevent untimely death. For example, one might engage in tests and treatments which are extremely uncomfortable in the short run in order to cure a fatal disease in the long run.

There is, obviously, a period of transition between the time when we hope to prevent untimely death — to cure the patient — and the time when relief of suffering is all that is available to us. The various people involved — patient, doctor, nurses, family — have to lose much of their faith in cure, and come to put more value in caring alone. In actual practice, the period of ambiguity in management sometimes extends well beyond the point when relief of suffering is the only reasonable goal, were we to step back and look at the situation.

Sometimes, therefore, our actions result in *neither* relief of suffering nor prevention of death. We find ourselves ordering uncomfortable diagnostic tests and treatments out of wishful thinking with little chance of cure, because we have not made the painful decision that cure is no longer a reasonable objective. After all, there comes a time when death is no longer considered untimely, all things considered.

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Relieve Suffering

What is the relief of suffering in a terminally-ill cancer patient? Physicians who have studied this suffering carefully, talking candidly with patients and those close to them, name four main components: pain, dyspnea, nausea and loneliness.

Pain is common in cancer. Probably pain is what patients fear the most about the disease. We have the medications to relieve even the most severe pain. But study upon study has shown that actual doctors, taking care of actual patients, often prescribe medication well below the doses necessary to relieve pain. Students of pain advise one thing — with substantial consensus — and we do another.

There are many reasons why we do not relieve pain properly. We are concerned that our patient not become addicted (in the few remaining days of life, mind you!). Perhaps we are skeptical about the severity of the pain. Sometimes we are making legitimate efforts to avoid pharmacologic risks with high doses of narcotics. Whatever the reasons, it seems that relief of pain is often not done well in our hands — relative to what we *could* do.

Dyspnea is apparently an awful feeling. In managing it, we should bear in mind that the perception of dyspnea mainly originates from activated stretch receptors in the chest — stiff lungs. Dyspnea is not what one feels because he or she is hypoxemic (although patients with dyspnea are often hypoxemic as well).

To relieve dyspnea, giving oxygen is not directly helpful, although it may be an effective placebo. Rather, dyspnea should be managed more directly, if possible, by attacking the anatomic problem in the chest — by thoracentesis, local radiotherapy and the like. Failing that, the mind-altering effects of narcotics provide relief.

Nausea is so often the result of chemotherapy. Do we give enough weight to its effects when we give palliative chemotherapy — that is, when relief of suffering is the main reason why the chemotherapy is being given?

Loneliness is the fourth form of suffering. We often put emotional distance between us and the dying. It is quite

natural to want to do so. One way we maintain this distance is to use the technical aspects of care as a device to avoid the real issues candidly. For example, we may spend what little time we have for our patient discussing laboratory tests and their results, or the technical aspects of treatment, rather than prognosis and feelings.

Unfortunately, the published medical literature usually does not provide the information we need to make humane decisions regarding pain, dyspnea, nausea and loneliness. Success and failure are usually described in terms of tumor-mass and survival, as if these were the only concerns. The state of the tumor is related to the state of the patient, of course. But the relationship is by no means very precise. The tumor may be regressing, while the patient is suffering or dying.

Seeing What Our Patients See

Suppose that we have made a clear decision that relief of suffering is all we are attempting to do. And we want to see what does and does not promote that. It would be naive to assume that we can simply clear our head and make accurate observations, as any fair-minded person could.

In general we do not — cannot — make observations altogether free of our own ideas about what should be seen. Epistemologists, philosophers of science who deal with the origin, nature and limits of knowledge, call this the "theory dependence of observation." Our observations are colored by the theories we subscribe to before we make the observations. As one scholar put it, "it often happens that when different disciplines look at the same thing (the same lines on the paper, for example), they *observe* different things."[1]

Figure 1 illustrates this problem. Some see in it a young woman, some an old woman. Both are correct.

To quote a scholar of this problem:

> "Note . . . how the cognitive orientation seems to give meaning to the lines or parts of the drawing rather than the other way around. Imagine what it would be like to be part of an interdisciplinary group [for example, a conference of patients, family, consultants, nurses and social workers] discussing a problem in which the young-old woman, or something analogous [e.g., importance of various symptoms, preference for treatment] played a part. What would happen if your discipline allowed you to see the young woman, while the other disciplines interpreted it as an old woman and you didn't recognize the difference? Would you be tempted to retreat to your own narrow discipline and categorize these other folks as just silly?"[1]

Our care of the terminally-ill cancer patient does involve many "disciplines": patient, family, physicians, nurses, social workers, and more. Each has his or her own perspective. Therefore we should be humble in our ability to see what is "really" there, and try extra hard to see things as the patient does and also as others involved in the patient's care do. The gap between you, patient, family, nurse and others may be wider than you think. As a result, you might be misled in assembling what you consider "the facts" for a management decision.



Death

How much suffering does death itself — the immediate process of dying — involve? To the living and healthy, the act of death seems distinctly unpleasant. It can sometimes appear grotesque in the final seconds — gasping respirations, seizures, and the like. But from everything we know, these occur after the patient is unconscious. What about the seconds leading up to death?

A vivid description of the moments before death is provided by David Livingstone, the British explorer. He wrote about a time when, for all intents and purposes, he was dying — in a violent, gruesome way, for that matter. He describes being attacked by a lion:

> "I heard a shout. Starting and looking half round, I saw the lion just in the act of springing upon me. I was on a little height; he caught my shoulder as he sprang and we both came to the ground below together. Growling horribly close to my ear, he shook me as a terrier does a rat. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake of a cat. It caused a sort of dreaminess in which there was no sense of pain nor feeling of terror, though quite conscious of all that was happening. It was like what patients partially under the influence of chloroform describe, who see all the operation but feel not the knife. This singular condition was not the result of any mental process. The shake annihiliated fear, and allowed no sense of horror in looking round at the beast. The peculiar state is probably produced in all animals killed by carnivora; and if so, is a

merciful provision by our benevolent Creator for lessening the pain of death."[2]

Where is the anguish, the fear and pain? Conspicuously absent.

This anecdote is backed up by more systematic studies of patients successfully resuscitated in hospitals. When asked to look back on their "deaths," their thoughts were contemplative, detached, even serene. Some expressed frustration at being brought back from the edge of death by cardiopulmonary resuscitation.

Thus, as best we can tell the immediate act of dying is not so arduous. In itself, it does not appear to be part of the suffering. We even know something about the mechanism for this. There appears to be a release of neurotransmitters, morphine-like substances and others, that change the mind set. Hence the title of the article about Livingstone: "Endorphins I Presume?"

The Decision Whether to Resuscitate

Now let us examine the decision to resuscitate. Here, in viewing the quality of our terminal care we need not evoke anything so subtle as the theory dependence of observation. Apparently we — or at least physicians like us — do not seek patients' opinions or guess what they want at all well. I will illustrate this with a study conducted at Harvard teaching hospitals in Boston, recently published in the *New England Journal of Medicine* (table 1).[3] The authors studied the decision-making process surrounding the care of 154 patients who were resuscitated in the hospital. The responsible physicians consulted patients' families about possible resuscitation only a third of the time; patients themselves were consulted less often. About a third of patients who survived resuscitation stated that they did not want it then, and would not want it in the future.

In the situation where cardiopulmonary arrest is anticipated some accurate information, for the purpose of relieving suffering, could apparently be obtained by simply asking the patient.

Terminal Care

How can we provide terminal care better in the days and hours before death? One view of it is provided by a study done in a community hospital in Washington state.[4] The terminal care of 30 patients, who died expectedly with cancer, was reviewed (table 2). Suffering was usually not relieved, but, more importantly, procedures were often performed that were unnecessary and increased suffering.

On a practical and constructive note, the investigator made the following suggestion: "The frequent occurrence, the quick onset, and the unpredictable timing of these problems suggest that physicians should write 'conditional orders' to relieve the symptoms, similar to CCU protocols."

Table 1
The Decision to Resuscitate in a University Teaching Hospital (154 Patients)[3]

	Percent of Patients
Physician formed prior opinion	68
Family consulted	33
Patients discussed with physician	19

Table 2
Terminal Care in a Community Hospital (30 Patients)

	Percent of Patients
Failure to relieve	
Pain	92
Nausea/vomiting	91
Dyspnea	100
Pulmonary secretions	93
Routine, slightly noxious unnecessary procedures	
Restraints	27
Suction	27
Frequent turning despite pain	43

Nutrition

The decision whether to provide nutrition to the dying patient is difficult to make on its own merits. The decision is tied up in a deeply-held belief that providing food and water is basic, humane care. Giving nutrition is emotionally compelling. But does it always do more good than harm, toward the goal of relieving suffering in an individual patient? This question was addressed in a recently published article entitled "Guiding the Hand that Feeds."[5]

The authors observe that "family members and health professionals sometimes project their own feelings onto the patient. . . . Judgments about the quality of life are best based on direct observation of the individual patient rather than on generalizations." The authors point out that although feeding is considered "ordinary," not "extraordinary," care, "all medical treatments, including tube feedings and the use of respirators [an example of "extraordinary" care], provide both benefits and burdens. The crucial issue is not the nature of the procedure but whether the benefits of a treatment outweigh the burdens for a particular patient. We suggest that in some cases the burdens of feeding may outweigh the benefits. Instead of being humane care, tube feedings may be painful, invasive, and impersonal for some patients."

The implications go beyond tube feeding to the common practice of urging food and water on patients who refuse them. Just how thirsty can a person be if he or she is alert and able to communicate, can swallow, is offered liquid, and refuses? How hungry can that person be if he or she refuses food, even their favorite foods, offered by a loved one? For many of us, the answer bears re-thinking. Sometimes we may add to the suffering of terminally-ill cancer patients by nagging them about food and drink.

Placebo Effect

The placebo effect is the relief of suffering by a means — for example, saline injections or sugar pills — for which the specific mechanism is not known. It is an old ally. But we consistently underweigh its value, and thereby forego a powerful tool in our armamentarium.

A simple expression of interest and concern, being in

control and holding appropriate optimism, can relieve physical suffering. I was reminded of this by a recent encounter. I went to visit a young woman with terminal cancer who had been hospitalized with yet another setback. I wondered, as I often do, what I could offer that would really be helpful. It seemed our conversation would be awkward, painful. But mother and daughter were pleased to see me. They recounted the events of the recent days; the patient described how she felt now. I just listened and asked a few simple questions, that was all. If any skill was involved, it was simply going in there and not being too ill-at-ease. And it seemed as if I *did* have something to offer! They were happier when I left — although there was no new diagnosis, and no better plan for treatment.

What can be learned — relearned — from this incident? The physician's presence is effective, in and of itself. There is a large, strong scientific literature to back this up, for those of you who doubt my experience, or your own. The placebo effect can be used to enormous effect to relieve suffering in dying cancer patients — at least, that's what the evidence suggest. Why doubt it?

Other Determinants of Clinical Decisions

Now what, more specifically, are these gremlins that interfere with our powers of observation, and hence the care of our patients? You are familiar with them. There are a great many. They distract us. They increase noise relative to signal, like static on a radio.

These gremlins are all the sorts of things that affect the practice of medicine, other than biology and caring. The following is an incomplete list and the entries are not mutually exclusive.

Time. Physicians are genuinely busy people. When we are with any one patient we are aware that others need us and could benefit from our efforts too. Only someone altogether unfamiliar with clinical medicine or otherwise unrealistic could regard the solution as "just try harder." So as a minimum, I would only suggest that we do what is simple, direct, and costs little *net* time. But we should not forget that many of the things we currently do, or ask to be done, are not useful and also take time. Some examples include arranging and tracking down the results of diagnostic tests when the need to know is small, and administering chemotherapy properly but for the wrong reasons.

Need for action. We are a society that is very uncomfortable with errors of omission — doing less than could have been done when things are going badly. On the other hand, we are quite tolerant of errors of commission — trying, even if things do not work out well. We want action. So we end up doing things for people, in the words of T. S. Eliot,

> Not for the good that it will do
> But that nothing may be left undone
> On the margin of the impossible.[6]

Sometimes we end up doing harm in this way. To the extent that we can extricate ourselves from the social values surrounding us, it is sometimes worth it for our patients.

Law. Of course malpractice law in this country reinforces this habit.

Money. The exchange of money also adds to our problem. Most medical care in this country is fee-for-service; we are paid more for doing more. Fortunately, medical care is still glued together strongly by sincerity and respect, decency and human values — on the part of doctors, patients, hospital administrators, and the rest. Imagine what it would be like if we all pursued our self-interest without restraint? But fee-for-service payment cannot help but have some effect on medical decisions.

One solution that has been proposed is prepayment. This method of reimbursement is growing in prevalence, and puts the economic incentive on doing less. What will be the effect on the care of terminally-ill cancer patients? While doing less sounds on the face of it like it would be bad for patients, prepayment could be an opportunity for good or harm depending on how we behave. Think back to the study of terminal care — how often patients in pain were bothered by turning and suctioning prior to death. How about high technology — CAT scans, etc. — in the last few days of life? Doing less of some of the things we do can be better.

There are other forces: religion, culture, guilt and the personalities of the individuals involved. All of these and more determine human values, and thereby our actions as physicians.

My message, then, runs as follows:

1) If the objective of care of the terminally ill cancer patient is to relieve suffering, and we are working with inaccurate information, inappropriate clinical (or ethical) decisions will follow. So we must try very hard to begin with sound information.

2) It is difficult to get accurate information — that is, from the patient's point of view — because "when different people look at the same thing . . . they *observe* different things." We must observe on our own, to be sure, but be humble and skeptical in our powers of observation. To improve our observations, we must reproduce the rigor of the scientific method, in a small way, each time we gather important facts.

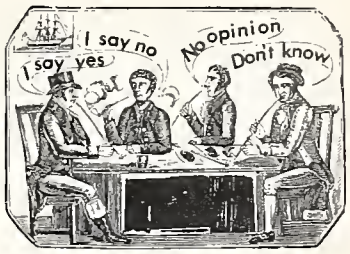
3) There is ample evidence that we often do act on inaccurate information in the care of terminally ill cancer patients. My illustrations point to some of the misconceptions we, or physicians like us, commonly have and how they might be avoided.

4) A great many forces other than biology — money, law, culture — determine clinical decisions. Sometimes they act in a perverse way; they can be a substantial distraction in the pursuit of our goals, to relieve suffering in human terms.

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Responding to Patients Who Refuse Life Saving Treatment



Eugene W. Linfors, M.D., editor

The question for February is: **How should physicians respond to patients who refuse life saving treatment (e.g., blood transfusions)?**

From Dr. Allen R. Dyer, a psychiatrist in Durham.

No physician has a right to treat any patient without the patient's informed consent. Legally this is governed by the laws of battery. A physician who treats without consent is committing an assault. Practically, one assumes consent when a patient comes asking for help and agreeing with what is proffered, but there are a number of situations where a patient may refuse treatment. This is their legally guaranteed right which should be respected by the physician, not only because it is legally required, but also because it is morally required.

The moral requirement is argued by philosophers as based on the principle of autonomy and self-determination. Any person, it is held, has a right to determine what happens to them because they are autonomous. Much has been written, especially in the past two decades, about the requirement of informed consent, which is designed to protect the patient's autonomy. The issue of informed consent, first developed in relationship to surgical procedures in the early twentieth century, received much attention during and after the Nuremburg trials because of involuntary experiments conducted by Nazi physicians. Recently the consumer movement has given impetus to such concerns with increasing objections to the "Doctor-Knows-Best" kind of paternalism.

There is a philosophical problem in arguing for informed consent on the grounds of patients' autonomy. What does it mean to be autonomous? If it means to be completely independent, few people meet that criterion. Actually consent must be (1) informed, (2) voluntary, and (3) competent (according to DHHS regulations), and so there is much room for interpretation. Nonautonomous persons, e.g., children, the senile, the comatose, and some psychiatric patients, deserve special consideration.

The matter becomes of practical importance when a patient refuses a treatment the doctor considers essential. The patient may seem irrational, even crazy. Such patients are especially frustrating to doctors whose personalities require them to be in control or who have difficulty having their judgment questioned.

A classic example of refusal of treatment is the Jehovah's Witness' refusal of blood transfusions (but not other medical or even surgical treatments). This refusal is based on religious grounds, an interpretation of a Biblical prohibition of the "eating" or consuming of a creature's life: "Only be sure that thou eat not the blood: for the blood is the life; and thou mayest not eat the life with the flesh" (Deuteronomy 12:23). While it may seem irrational to many physicians, Jehovah's Witnesses regard it as an article of faith and a particular test of one's adherence to God's Law. Thus it may be easier for a physician or surgeon to empathize with a Jehovah's Witness' refusal of blood if one appreciates the patients' belief system. The risk of death may not seem so bad compared with an eternity of damnation.

Practically, the matter may not be as simple as letting the patient decide for himself. The doctor may be forced into attempting surgery without the possibility of blood transfusion. The doctor may be tempted to insist on conditions that would make his own task easier. The doctor may be tempted to refuse to treat the patient if the patient does not comply with the doctor's wishes. Obviously such conditions do strain the physician, but most would probably try to respect the patient's wishes and do what is possible under the circumstances.

Somehow these situations often turn into heated confrontations, challenges to the physician's authority, control struggles. At another level the patient may be more concerned with pressure from other church members and might actually welcome alternatives such as certain blood products or plasma expanders.

The issue of children is a special case. Children are not considered to have the right of refusal (or assent) since they are not autonomous and have not reached the age of reason. Hence parents must consent for them, and if the parents do not consent to a treatment that the physician deems necessary, the physician may seek a court order. This is actually fairly routine even in middle-of-the-night situations.

Another group of patients that is not considered autonomous (competent) are those with mental disorders. The question of the legal rights of committed psychiatric patients to refuse psychotropic medication is a complicated one, which is not settled legally. It can become a practical question for the physician with a patient who has become depressed and who may prefer to die (or profess to) rather than continue with treatment. This is not uncommon with renal dialysis patients, cancer patients and others. It gives rise to the "Whose Life Is It Anyway?" debates popularized in the play and movie by that name. Such patients do

have the right to refuse treatment, but they should not be allowed to exercise that right without the benefit of psychiatric consultation. It is possible that their depression can be treated, and that they would feel different about the decision were they not depressed. Often with such patients part of their depression provokes rejection in those who are caring for them, who may feel that their efforts to help aren't appreciated and feel tempted to let them have their own way out of frustration. Here, as in so many cases in medicine, the psychiatrist's concept of "therapeutic alliance" becomes extremely important. The doctor must have the patient's trust for any treatment to be successful. Without such an alliance, even the best treatment plan may be subverted either actively or passively through noncompliance.

Patients have both a legal and a moral right to refuse treatment, which the doctor has an obligation to respect. But the doctor also has an obligation to try to help the patient in whatever way possible, and this may mean not rejecting the patient who rejects us, but seeking with the patient alternatives that may be acceptable to both.

From Dr. H. J. Proctor, a surgeon in Chapel Hill.

I believe that individuals who are of legal age and mentally competent should have the freedom to control their own therapy. Even more specifically, with regard to individuals such as Jehovah's Witnesses who refuse blood transfusions, I believe that physicians should honor the religious beliefs of their patients. Consequently, I have no qualms about caring for Jehovah's Witness patients, and I will not transfuse blood products against their wishes, even if this means the death of the patient. In point of fact, this is rarely the situation since it is an unusual Jehovah's Witness patient whose hemoglobin levels sink to the point below which they cannot compensate by increased extraction and increases in cardiac output. As far as mentally incompetent patients or legal minors are concerned, I do not feel that another individual's beliefs should be inflicted upon them and accordingly if I felt that a blood transfusion was in the best interest of the patient I would proceed to get court authorization to treat the patient in what I felt was the most appropriate manner. Lastly, as a physician, the responsibilities I feel toward my patients are medical, ethical, social, religious, and legal in scope, and I would defend the right of any physician, once a contractual arrangement has been made with a patient, to do whatever he or she feels is appropriate.

From Dr. Harold R. Silberman, an emergency medicine physician in Durham.

No single event in the doctor-patient relationship polarizes each into a power struggle more than a Jehovah's Witness refusing blood products during a serious medical or surgical illness. That apparent loss of cooperation between the two individuals, with its attendant rigid overtones, based on the one hand upon religious beliefs and on the other hand upon medical conviction, often infuriates the physician. At the other end of the spectrum of refusal of therapy are those individuals whose addiction and/or lack of will power interfere with following instructions. And, after all, instructions to abstain are often more important than many things we prescribe in a bottle or syringe, and many bad habits are self destructive.

Between these two extremes is a range of noncompliance that includes: not filling prescriptions; taking less of the drug than prescribed; not keeping appointments; refusing to follow instructions about self monitoring (as in diabetes); and taking medications (usually over-the-counter) specifically proscribed by the doctor. Because this type of behavior goes on over many years it doesn't carry the stigma of a sudden decision to refuse a critical treatment.

Younger but sometimes even older physicians also become irate and thereby less effective when a portion of the physical examination is declined or a proposed test, such as an LP, is declined.

But there can be another, somewhat more subtle area of disagreement or conflict. It occurs when the patient is advised to undergo a procedure or therapy that is not temporally critical, *may* not be life saving, carries some risk of significant side effects, and is projected to be demanding in time and cost. Such a situation can develop in many settings but perhaps more frequently when dealing with cancer. Therefore, while advising post graduate fellows who are training in oncology, it's been my habit to teach the principle that *not every* patient is capable of participating in an aggressive cancer research protocol, even when it's explained that such, though novel, represents the *best patient care* of the day. For example, how many individuals with acute non-lymphocytic leukemia can understand, much less handle, the concept of a bone marrow transplant that carries some risk of immediate death, without ever returning home; a significant expectation of serious continuous side effects for a large fraction of patients who survive the transplant; and less than a 40% chance of permanent cure for anyone?

When dealing with more sophisticated and braver patients, it's not unreasonable to ask: "How much of your personal resources do *you* want to expend battling this illness?" Because Americans put such a high premium on saving/sustaining life, it sometimes stuns the physician when a patient decides against doing so.

Once we accept the fact that patients may and do go against our best advice, there are five critically important things to remember when negotiating in a setting where someone is refusing life-saving treatment. First, confrontations or power struggles are usually "no-win" situations for all concerned. Second, even when seriously ill, the adult needs to be treated like an adult, not like a child — we are not everyone's father nor are we God. Third, there is a real difference between a patient being incompetent and showing poor judgment. Incompetent folks may and often should be placed under someone's jurisdiction whereas people who make what we label poor decisions can neither be restrained or incarcerated. No where else in the medical system than an emergency room does this concept require more understanding. An angry, demanding, impatient,

wounded or hurting adult may elect to sign out AMA (against medical advice) whereas if inebriated, that same person should be restrained, studied and appropriately treated when it's a life-saving emergency. Fourth, managing the so-called difficult patient can be a significant psychological stress to the vulnerable physician. In this regard, its been comforting to rationalize that if one is mostly consumed by a single interaction, there's little left for the patients that follow. Fifth, all of us need to gain more humility by remembering clinical vignettes. There are heroin addicts who have left hospital short of completing the prescribed course of antibiotics for SBE and yet are cured. Pancytopenic patients have declined hospitalization to stay home because a child is coming for a visit and yet they didn't hemorrhage to death or become septic.

The care of the physician troubled by such refusals and rejections is also a major consideration requiring our attention. Unfortunately, unless s(he) develops a philosophical attitude, frustration will be intense. Many of the desirable character traits that contribute to an MD's success can become risk factors for depression when amplified by an apparent failure in a given case. Amongst the topics said not to receive enough attention in medical school are the psychological vulnerabilities of physicians. At least we should teach each other that it's "o.k." for a patient to say no!

A careful look at the special challenges created for the surgeon and internist by a Jehovah's Witness is exemplary of the subject under discussion. Members of that faith accept medical/surgical treatment but are deeply religious believing that transfusions of any autologous whole blood or components thereof is forbidden by several Biblical passages: "Only flesh with its soul — its blood — you must not eat" (Genesis 9:3-4); "you must pour its blood out and cover it with dust" (Leviticus 17:13-14); and "abstain from . . . fornication and from what is strangled and from blood" (Acts 15:19-21). Usually Witnesses recognize that such convictions can add risks to and complicate their care. Nevertheless, it's clear that they want/expect a voice in that care and hope that their physicians can understand an axiom: no one truly benefits if the corporal malady is cured at the price of compromising spiritual life with God.

Rather than bemoaning "this patient has tied my hands," some of us can choose to see the situation as only one more complication challenging our skill. All too often medical personnel are worried about their liability when they should be thinking about the patient's rights to make decisions about his body and his life.

Why does any of this matter? It matters because these principles, sometimes ethical and sometimes not, pervade medicine and can be critically important in the late stages of chronic disease. Once it becomes obvious that you are truly concerned, easily approached and listen well, you will find many patients who are ready to stop or forego a treatment. They've just been waiting for their physician to give them permission.

From Dr. Lucien S. Wilkins, a gastroenterologist in Wilmington.

A physician dealing with the issue of a patient's refusal to accept life saving treatment (e.g., blood transfusions) may be dealing with an age old issue involving patient's rights and physician's responsibility but the arena today is different as there are right-to-life groups, government agencies, legal precedents and disagreeing family members all wanting to be heard. The new arena increases the pressures, opens up options, but does not change the basic process of solution.

The solution is, in my opinion, straightforward: (1) communication, (2) education, and (3) consultation. I have intentionally omitted litigation, as that form of interference with the doctor-patient relationship should occur only when all reasonable solutions have failed.

Whole blood transfusion is controversial both on scientific and ethical grounds. Whole blood is a fixed dosage combination drug with potential side effects and a form of organ (blood) transplantation which opposes deep-seated religious beliefs of some.

Step one for the physician after hearing of the patient's refusal to accept the life saving treatment is to *sit down* with the patient and make certain you have clearly communicated the benefits and the consequences of the planned therapy.

If an impasse is still present, alternative, less objectionable therapies should be considered. Sometimes less therapy may be no less desirable. An alternative to transfusion might include i.v. saline to expand the volume, recumbency to decrease the need for volume, and iron for anemia.

If alternative therapies are considered not to be in the patient's best interest, the physician has two choices, either consultation or referral.

If referral occurs the physician may have solved his problem but the second physician is still at the same point in the decision making process. For either physician the next step is consultation. Ask for help!

Consult with a specialist in the problem area. A hematologist/oncologist, in the case of the patient who refused transfusion, would be most helpful as undoubtedly he has encountered this ethical problem before due to the nature of his practice. If a specialist is unavailable, go to your department chairman, who according to most hospital bylaws, is responsible for all practice matters within his department and should lend you support.

If your hospital is one of the 10% of American hospitals with an Ethics Committee composed of MDs, nurses, administrators, lay people, and hospital lawyers, you have a support system to assist you with your dilemma. They are there to support you in an ethical crisis in the same way the CPR team supports you in a medical crisis. They are not there to legislate ethics or to take the decision making away from the physician and the patient but to enhance the decision making process.

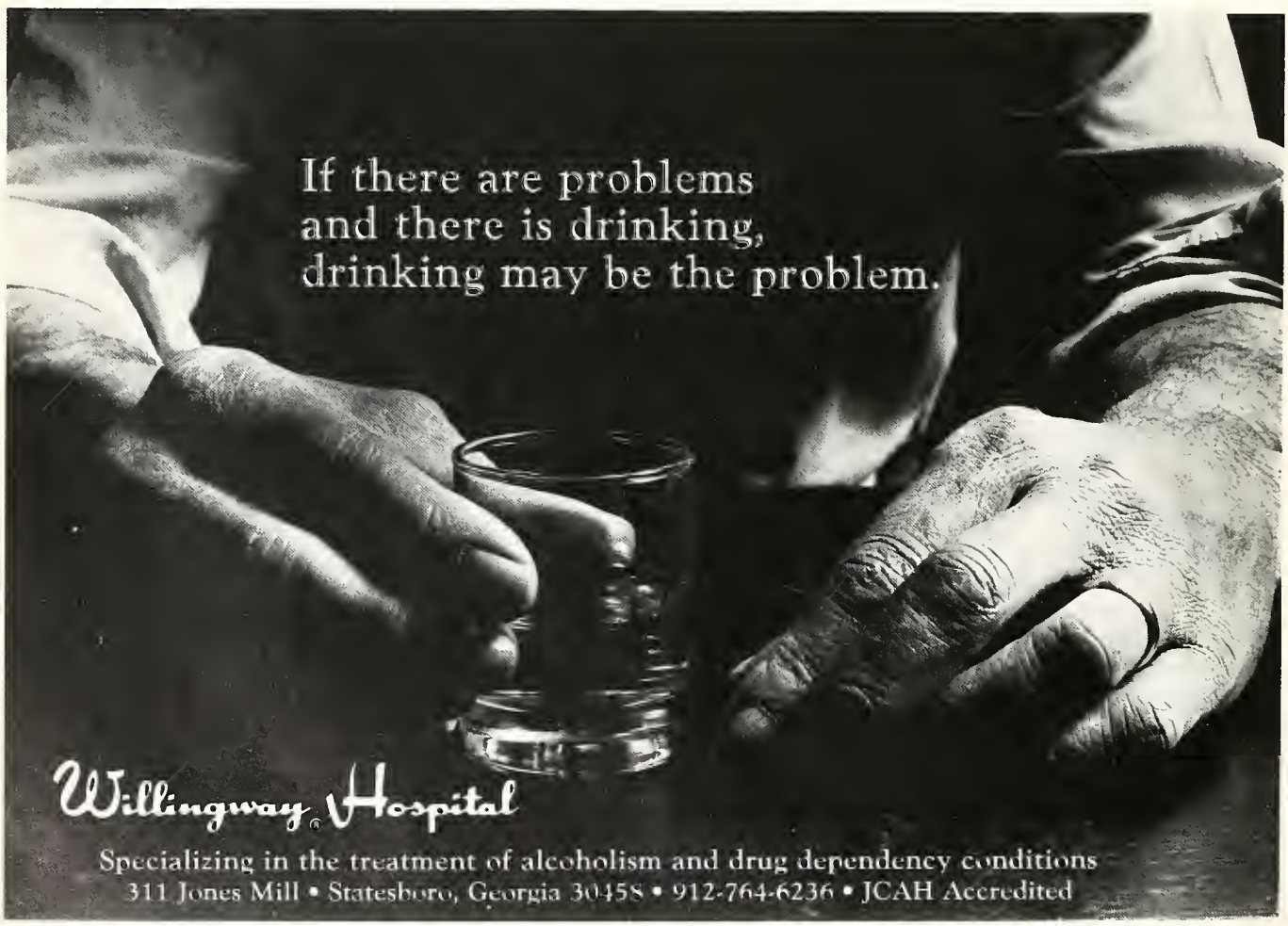
The above process may not solve the issue at hand but reaching a reasonable solution is more likely.

• EDITOR'S NOTE: Lots of good advice here, both philosophical and practical. The message seems to be to listen to the patient — not only his complaints, but also goals and values — before offering treatment. Sharing responsibility with patients will make some, but not all, decisions less difficult.

We are changing the format for the Forum slightly. Henceforth we will announce the next question of the month at the same time as we publish the responses to the current question. We invite readers to respond with opinions — short or long — to me. We will review them and publish as many as possible. We will also continue to ask others by mail to respond. We hope this will provide an even greater diversity of opinions for the Forum.

The next question for the Forum is **"In your personal opinion, does the refusal of precertification for admission to the hospital by insurance companies constitute the practice of medicine? Should they be held liable for malpractice?"**

May we have your response by February 22? Our address is Box 3910, DUMC, Durham 27710.



North Carolina Medical Journal

Features for Patients February 1985

Welcome to the Helicopter Wars

The Development of a Helicopter Emergency Medical Service for Eastern North Carolina

Nicholas H. Benson, M.D., Christopher J. Mansfield, M.S. and
E. Jackson Allison, Jr., M.D., M.P.H.

As of the summer of 1984 there were approximately 80 hospitals in the United States with a helicopter emergency medical service based at their facility as part of an integrated trauma service and inter-hospital transport service for critically ill patients. These hospital-based helicopter emergency medical services (HEMS) typically involve the lease of a utility or executive helicopter retrofitted as an advanced life support (ALS) ambulance. The aircraft is operated and maintained by personnel supplied by a flight-service vendor but staffed with emergency medical personnel supplied by the hospital. The aircraft, pilot and medical team are stationed at the hospital and are immediately available to respond to trauma incidents or requests for the transfer of critically ill patients from one hospital to another on a 24-hour-a-day, seven-day-a-week basis. This paper relates the developmental process of such a service to serve the citizens of eastern North Carolina at Pitt County Memorial Hospital in Greenville.

From the Department of Emergency Medicine and the Center for Health Systems Research & Development, East Carolina University School of Medicine/Pitt County Memorial Hospital, Greenville 27834.

Background

The first hospital-based program in the U.S. was initiated in 1972 at St. Anthony's Hospital, Denver, Colorado. The development of 80 or more similar programs in the ensuing 12 years is remarkable. In addition to the hospital-based programs, there are about ten privately-operated and four state-operated helicopter emergency medical service programs.

While services operated by Norfolk General Hospital (called "Nightingale") and Roanoke Hospital in Virginia provide some service to North Carolina residents within the effective range of their helicopters (70-100 miles), most of the citizens of North Carolina are without access to such a service. This is likely to change, however, as Pitt County Memorial Hospital and Duke University Medical Center are both in the process of developing hospital-based helicopter services. Other hospitals in North Carolina and many in other states are considering such a service. The state of North Carolina has designated a statewide task force to investigate the feasibility of creating a state-operated service.

Much can be learned from those who have gone before in this endeavor, and there has been a unique willingness on the part of personnel in existing programs to share their insights and experiences with individuals developing new programs. There is enough at stake financially, and there is sufficient complexity in developing a high quality service, for any hospital to be advised to proceed with cautious objectivity and thorough planning. While many hospital and medical personnel have had some tangential military experience with medical aviation, the development and administration of a complete program is not a simple task. (Unfortunately, the multitude of differences between military and civilian services makes expertise in the former of only marginal utility in the latter.)

Helicopters are expensive to buy ($.5-$1.5 million), operate and maintain. Their primary virtues are speed and access to areas not reachable by ground ambulances. They are neither medical nor therapeutic devices in themselves, but they can be used effectively to quickly extend a hospital's emergency medical and critical care capabilities to patients who are critically ill or injured. They

can quickly transport patients to and between the most appropriate resources of the health care system. The medical personnel who are carried to, or with, the patient are essential. They may be physicians, critical care nurses, paramedics, or respiratory therapists. A variable combination of any two of these health-care professionals may be carried on the helicopter, depending on mission and staffing patterns.

While most helicopters in EMS use are capable of carrying two or more patients, most missions transport just one patient. Data derived from a survey of 22 programs operating during 1982 suggest that two-thirds of all flights are hospital-to-hospital transfers; in one-third of flights the patient's origin is the scene of an accident.[1] The same data reveal that, regardless of origin, 44% are trauma victims, 15% are cardiac victims and 4% are burn victims. The remaining are critically ill medical, 20%; neonates, 13%; and high-risk obstetric, 4%.

The need for and efficacy of rapid intervention in critically ill patients are generally accepted. The need for and efficacy of rapid intervention in trauma cases have been extensively documented. Though the potential of death from trauma depends upon the severity of illness, timely intervention and quality of care are essential. **Time to treatment is a critical factor.** In the last 15 years there have been numerous reports and studies supporting the importance of rapid stabilization and definitive care. Stephany concludes that while 20% of all fatalities are instantaneous, 26% of all non-instantaneous deaths have a potential for survival; furthermore, fully half of these non-instantaneous deaths occur within the first 60 minutes after the accident.[2] R Adams Cowley, director of the Maryland Institute for Emergency Medical Services, draws similar conclusions and describes the **first 60 minutes as "the golden hour"** for delivery of trauma care.[3] Extensive experience by the military in Korea and Viet Nam support these findings for combat-related trauma.

The efficacy of the helicopter ambulance carrying personnel trained in advanced life support has been proven in both military and civilian applications. It serves both to bring more advanced medical care to the patient and to reduce time to definitive treatment, such as surgery. Experience of hospital-based helicopter ambulance programs during the last five years suggests that 20% of all patients transported by helicopter otherwise might have died,[4] which is similar to that in West Germany where a network of 32 air-rescue helicopters has been credited with a reduction in motor-vehicle mortality of 25 percent.[5] Baxt and Moody claim a 52% reduction in predicted mortality of patients transported by helicopter in San Diego.[6]

Helicopters are valuable only if the patient is transported to an institution capable of providing the appropriate level of care. Their value over ground vehicles increases in proportion both to the time saved in transport from site A to site B and to the level of care provided en route. The helicopter is of maximum use in linking the rural accident scene or hospital with the tertiary-care trauma center at a distance of 70 to 100 miles.[7]

The helicopter, because of its greater speed and the fact that it can travel in a straight line, can cover an area equivalent to that covered by 11 ground ambulances with response times equal to the helicopter.[8] Studies have shown that to equip and staff one ground ALS unit costs in excess of $175,000 per year.[4] If this figure is multiplied eleven times, the expense of a helicopter program can be less than that for corresponding equivalent ground coverage. If multiple Level I or Level II Regional Trauma Centers are also necessary for equivalent service, economic advantage increases in favor of the helicopter even more. Consideration of refining and maintaining skill levels of advanced cardiac and trauma life support personnel also is an argument against duplication.

The Planning Process

With the above understanding we were led to ask the questions "Could a hospital-based HEMS work in North Carolina?" and, more specifically, "Should there be a service for the eastern part of the state at Pitt County Memorial Hospital?"

Looking at the shape and size of North Carolina (500 miles East to West by 100-180 miles North to South) and considering the effective service area radius of a helicopter to be 70-100 miles, it was apparent that at least three programs would be necessary to cover the state geographically. Greenville happens to be about 100 miles from the eastern-most portion of the state (Hatteras) and in the middle of a non-circular health service area (North Carolina Health Systems Agency VI) of 15,000 square-miles and 1.04 million people. Because of the geography and the fact that Pitt County Memorial Hospital (PCMH) is a Level II Regional Trauma Center and the site of the emergency medicine residency training program at the East Carolina University School of Medicine, it seemed logical that one of the HEMS programs should be at PCMH. However, could it be justified financially? Could the trustees of the hospital be convinced to support it?

Considering the population bases claimed as service areas of other programs as an initial rough indicator of need, we found that other programs served areas of as few as 95,000 people and as many as 10,500,000. The average was 1,500,000 per helicopter; thirteen of 59 programs (22%) had fewer than 1,000,000 in the service area.[1] A circular service area with a 100 mile radius for a HEMS program based in Greenville would contain well over 2,000,000, since the Research Triangle area and Wilmington would also be included (figure 1). It was decided that residents in the Research Triangle area would not likely be users (due to the proximity of local Level I Regional Trauma Centers at Duke and U.N.C.) but that some residents of New Hanover, Bladen, Pender and



Figure 1. *A map of North Carolina and Virginia showing 100-mile radius circles around existent programs in Norfolk and Roanoke, Virginia and proposed program in Greenville, North Carolina.*

Sampson counties would; including these four counties as a secondary service area would add another 200,000 people to the proposed service area. However, it was apparent that some patients in the northeast portion of the state would continue to be served by the program in Norfolk; balancing the added utilization of a secondary service area against those patients lost to Nightingale from the sparsely-populated northeast resulted in a projected net service area roughly approximating the health service area of eastern North Carolina defined as NCHSA VI.

The feasibility study was undertaken (a) to estimate the cost of the proposed service; (b) to ascertain the demand for the service; (c) to estimate the revenues to be derived from accommodating that demand; (d) to compare cost with revenues; (e) to evaluate risks and indirect benefits; (f) to evaluate alternatives; and (g) to present it all within the context of the mission statements of Pitt County Memorial Hospital and East Carolina University School of Medicine.

Estimating the approximate cost of the service is relatively straightforward; estimation of demand is not so easy. A true needs assessment conducted in this area would involve the identification of the types of trauma and medical conditions that would benefit from rapid transport, defining the incidence of these conditions, applying them to the service area population and thereby estimating the need.

Some conditions that would be appropriate for transport by a helicopter might be:

1. Multiple trauma
2. Burns
3. Spinal cord/head injury
4. Distressed neonates
5. High-risk perinatal
6. Unstable cardiac problems
7. Unstable aneurysms
8. Intraaortic balloon pump patients
9. Streptokinase candidates
10. Reimplantotion candidates
11. Organ transplant candidates
12. Other critically ill or injured persons

But no one knows the incidence of these conditions with enough accuracy to make estimates of need; nor do we have any accepted methodologies for defining what percentage would be realized demand, particularly in eastern North Carolina. The best we could do (and the best any other program sponsors have done to our knowledge) is to estimate demand based upon other programs' experiences.

Data of the American Society of Hospital-Based Emergency Air Medical Services (ASHBEAMS) and the Annual Program Statistical Survey published in Hospital Aviation[9] suggest that the mean utilization for 57 programs surveyed in 1983 was 63 patients transported per 100,000 population (the number of patients is roughly equal to the number of missions). The range of utilization was from 3 to 363 per 100,000 and the median was 43. Because of the extreme range, the median would normally be the most appropriate average to use but since 23% of the programs were new within the year and 47% were less than two years old with assumed lower utilization, the higher (mean) figure seemed appropriate to use as a guide for estimating the level of demand which would be experienced after the first year of operation in eastern North Carolina.

Applying this rate to a service area comprising all of eastern North Carolina (HSA VI) and having a population of 1,038,273 produces a projected utilization of 654 patients annually. Experience of other programs allows us to estimate that during the first year utilization will be about 60% of this figure (or 400 patients). Full utilization may be expected in the second year.

Of the 654 patients transported, we estimate that two-thirds (or 438) would be received at Pitt County Memorial. Of these, 80% would represent new patients, i.e., 351 new patients who would not have been admitted to PCMH otherwise.

Having arrived at some idea of volume of service to be provided, we then proceeded to identify the variables and determinants of revenues. Using information from existing programs, we estimated percentage source of payment and individual source collection rates. In the aggregate, we concluded that we might experience about 75% collection considering this to be a new program in North Carolina but trusting that significant precedent had already been set with similarly expensive ground transport. Assumptions also had to be made about how much we could charge for the service. Many of the

existing programs charge substantially less than cost (typically about half) and make up the difference via their margin on additional inpatient revenue. Our inclination was to avoid the cost shifting and charge what the service would cost at projected full utilization ($1200-1300 per flight); to be safe, however, the break-even analysis was based upon a charge at only 75% of cost.

The cost was relatively easy to project and we figured it to be about $765,000 for the first year, 86% of which would be fixed costs representing a flight service lease and personnel commitments. Variable costs would be hourly use charges for the helicopter, fuel and supplies.

The break-even analysis was accomplished using an electronic spreadsheet and factoring in the effect of additional inpatient utilization with assumptions made about patients' length of stay and inpatient marginal cost. The electronic spreadsheet allowed considerations of many different combinations of assumptions about the variables. Trying all the worst-scenario assumptions about the variables used to create expenses and revenues, we were able to conclude that the program would be financially feasible.

Before proceeding, however, we reviewed and evaluated the alternatives to this endeavor. The possibility of equivalent service with multiple strategically placed ground ALS ambulances was ruled out on the basis of cost for PCMH to do this alone and lack of a consortium or regional entity to organize such an undertaking. The possibility of multiple trauma centers was also ruled out for similar reasons. The Military Assistance to Safety and Traffic (MAST) program was reviewed, but military priority and response times do not make this program an equivalent service in eastern N.C. Similarly, an aeromedical program within the state's law enforcement and/or transportation departments was considered but felt to be less desirable for the reasons of conflicting user priorities, response times and uncertainty of eventual development. Prevention was considered as an alternative, as well. While we know that most of the trauma and illness to be transported by helicopter is preventable and we feel strongly that it could be, society's resources and collective will have not been focused in that direction. Finally the risks and indirect benefits were reviewed.

The Development Process

Based upon the research related above, it was clear that a helicopter system would be extremely beneficial to the citizens of eastern North Carolina. It was viewed as a way of upgrading the ability to deliver high-quality advanced life support health care to critically ill and injured persons in the area, i.e., a way of extending the capabilities of the tertiary medical center to benefit the entire region. The hospital board received and reviewed our feasibility study; then they approved the program for a provisionary year, which is believed to be sufficient time to prove its medical and financial worthiness.

The Certificate of Need Application for the acquisition by lease of a helicopter service was submitted in May 1984. Having received approval from the Eastern Carolina Health Systems Agency in July 1984, we then awaited final approval from the North Carolina Department of Human Resources' Division of Facility Services, which was expected on or before October 28, 1984.

Working under the assumption that the CON would meet with approval, we next proceeded to deal with the process of selection of a vendor. Inasmuch as the vendor supplies the hospital with not only the medically retrofitted aircraft, but also the pilots, mechanic, scheduled and emergency maintenance, certain aspects of insurance coverage, and experience in marketing and program management, this is a decision of utmost importance to the success of the program. These vendors, for the most part, are involved with multiple civilian industries utilizing helicopters in addition to EMS work; these industries include logging, mining, rescue operations, fighting forest fires, and servicing off-shore oil rigs. The health-care area is a relatively new opportunity for involvement, having really developed over the past five to ten years. Some of them have extensive experience in hospital-based services; others have had only a few contracts for a limited period of time. While the former group brings years of experience and insight to the area, the latter group tends to offer lower bids to programs in the hopes of increasing the number of their hospital contracts. These factors of price to the hospital and experience of the vendor are of extreme importance. Further significant particulars include availability of "back-up" aircraft from the vendor (so that the program can remain operational when the hospital's helicopter requires maintenance), their maintenance record at other programs, the quality of mechanic and pilots they provide, and their administrative and financial solidity. In the final outcome, however, most public hospitals are still required to do a request for proposals and take the lowest bidder that meets their needs.

Selection of a particular helicopter for a program is yet another area that can be problematic. While this is much too complex a topic to discuss in detail here, some of the factors that need to be considered include the numbers of patients and attendants transportable; the speed, maneuverability and lift-power of the craft; the flying radius (without refueling); room in the aircraft for patient care; reliability; ease of maintenance; and cost. Some vendors, rather astutely, maintain that the hospital should work on medical parameters and marketing, leaving the choice of aircraft up to them; these authorities maintain that while the hospital officials are knowledgable in both medical matters and concerns about the local area, the vendor is the chosen representative of the helicopter industry and is more experienced in deciding which aircraft is best suited to local needs.

A third portion of the program that must be handled with great care to ensure a success is the flight team, i.e., those people who will deliver the health care in the air. A major decision in this realm is what types of professionals the team should consist of: physicians; physician-assistants; flight nurses; or paramedics. This decision will be made largely by preexistent realities. For instance, at PCMH there are not adequate numbers of physicians trained comprehensively in all aspects of critical care to staff both hospital and helicopter; nor do we have available to us paramedics with appropriate street experience. Thus, we have decided to fly two registered nurses; the exception to this is that flights for neonatal transports will use representatives of the hospital's standard neonatal transport team.

Selection of these flight nurses (FN), especially the chief flight nurse (CFN), requires a thorough search for persons with demonstrated excellence in critical care, an ability to react calmly and diplomatically in chaotic and stressful situations, strong experience in management and teaching, and a knowledge of prehospital care. These persons serve as extensions of the hospital's critical care units; they must be trusted to perform in an exemplary fashion under any conditions. Once selected, they need to undergo rigorous and comprehensive training to cover all aspects of the program; this includes, but is not limited to, advanced cardiac life support, advanced trauma care, cardiopulmonary emergencies, neurological crises, pediatric emergencies, high-risk obstetrics, altitude physiology, flight safety, extrication and immobilization, and radio communications. Part of this intensive training regimen should include onboard drills utilizing the equipment and cramped quarters of the aircraft. The quality of care that they deliver at a hospital or scene will have an overwhelming impact on whether the program gets further calls from that source.

Other principal members of the team must include a medical director with a strong background in emergency care, a program administrative director with agility in marketing, and dispatchers with EMT training to provide 24-hour staffing to a communications-dispatch center. (Note that often the CFN and the program director are the same person.) The team does not stop here, however; the program could be doomed to failure without the backing of the medical center's entire medical and nursing staffs, hospital administration, all ancillary departments, and all support personnel. All persons in the medical center community, from the chairman of the board of trustees to the groundskeeper who sweeps off the helipad, must lend their firm support.

A helipad close to the emergency department, a flight operations center (to include office space for staff and sleeping quarters for pilot), and a communications post with full UHF and VHF radio equipment along with equipment for continuous weather surveillance and recording of incoming calls and radio transmissions are vital.

While the flight team should be in nearly constant contact with medical personnel at the base hospital, it is necessary to have a complete set of policies and protocols to utilize as conditions dictate. This allows for appropriate care whenever radio contact might be lost, as well as assurance of adherence to a defined standard of care. It also provides guidelines to follow when the unforeseen arises; for example, what should the flight team do if they are on the way to another hospital to pick up a patient and they fly over a small plane which has crashed in a forest and no help for the pilot is in sight? Should they stop? Should they complete their primary mission?

The CFN and program director must create a system to maintain records of all aspects of all flights. This allows for evaluation by the CFN and the medical director of the quality of care rendered, data retrieval for audit and evaluation, appropriate follow-up reports to the referring agency and billing purposes. Since this is a relatively new dimension in health care, one of the unspoken requirements of all programs is to participate in research and data collection activities designed to justify the use of this high-cost modality and to ever-improve the quality of care available to all patients.

A recurring theme in advice from existing programs is one of marketing and public relations. Most programs start in an area that has never seen such a service before; therefore, it is incumbent upon the people in the program, even before they start taking patients, to illustrate to the potential referring agencies how and why they can aid them. This marketing may take many, many forms: presentations to hospital medical staffs; discussions with EMS, police and fire squads; displays at fairs, conventions and shopping centers; mailings of brochures, bumper stickers, telephone stickers, and buttons; participation in the electronic and print media; and outreach education programs on CPR, basic first-aid, etc. In addition to letting people know that the service exists, marketing must include information on how to access the service. People must know who can refer a patient, how to call the helicopter, and what types of patients are appropriate for the service. Beyond this, the potential referring agencies need to know where in their area a helicopter can land, how to make that landing area safe, and how to deal with the helicopter and crew during take-off and landing.

A positive public relations campaign is especially vital in dealing with local prehospital care providers. They must understand that the service is there to help them provide for a patient who is beyond their local capability, i.e., that the service is there to complement their abilities but not to supplant them. An image of help to the general community, of friendly and gracious cooperation with local agencies, and of delivery of excellent medical care to the critically ill or injured is paramount.

Conclusion

We received approval of our CON on October 26. Our request for proposals went out to the vendors in late August; the bids were opened in mid-September. We have filled the Chief Flight Nurse position, and we are now actively recruiting Flight Nurses. We hope to keep steadfastly to our timetable, which calls for initiation of training and coordination flights to referral agencies in early winter and availability for patient transport in early April 1985. In late September, PCMH was notified of the formation of a legislative study commission to investigate a statewide Highway Patrol-sponsored system with dual law enforcement-medical missions as a result of the statewide task force previously mentioned. At their final meeting in late November, this group decided to promote a bill to appropriate funds for the development of a statewide HEMS to be operated by the North Carolina Office of EMS.

The future of hospital-based EMS helicopters in this country is most promising and equally exciting. The number of programs shows potential for nearing 100 in a year or two. The proliferation of research and patient-care improvements should have a global impact on medical care. It becomes increasingly vital for programs to work together and to avoid competitive displays. Only through consistent and exhaustive evaluation of our methods and outcomes can this industry continue to strive to attain the excellence in patient care that is our goal.

The authors are deeply indebted to Ms. Joni Farmer for her ever-cheerful secretarial support.

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Duke Takes the Plunge

On March 1, 1985 Duke University Hospital will initiate a Helicopter Emergency Medical Service (HEMS). The helicopter will be based at the hospital, on a pad immediately adjacent to the emergency room entrance. Weather permitting, the helicopter will respond to calls 24 hours a day, 7 days a week.

On each flight, the helicopter will be staffed by a pilot and two nurses experienced in critical care or emergency services and specially trained for HEMS. While caring for patients in flight, they will be in constant contact with Duke physicians involved in the delivery and management of trauma and other critical care services.

The helicopter will be operated by a company chosen for its wide and successful experience in the operation of helicopters. The company will provide a Bell 222UT specially configured and equipped for EMS, pilots, a mechanic, maintenance, and a backup craft.

The service will transport patients who require immediate transfer to a tertiary care center. Typically these will be patients threatened with the loss of life, limb, or function as a result of

- life threatening trauma
- cardiac or respiratory emergencies
- acute pediatric medical emergencies
- acute surgical emergencies
- major thermal injuries

Patients will be transported to Duke Hospital, or to another tertiary care center when appropriate, feasible, and requested, and when the receiving hospital has agreed in advance to pay the cost of the flight.

The service will respond to calls coming in over a dedicated WATS line from other hospitals, from physicians, from police and emergency services, and other authorized agencies and individuals. The service will not compete with but will supplement ground ambulance transportation and other HEMS programs that may develop in North Carolina. It is anticipated that 80% of flights will transfer patients from other hospitals to tertiary care; the other 20% will evacuate patients from accident scenes and other points of need.

The Bell 222UT can fly more than 400 miles without refuelling, but the effective operating range of the service will be within 150 miles of Durham. Beyond that range, the advantage of the helicopter's speed (150 mph) is offset by distance. A range of 150 miles will allow service to 77% of North Carolina's population and all major cities except Asheville.

Operation of the service will cost $1.2 million per year. Variable cost — for helicopter operation, fuel, and supplies — will account for $200,000. Fixed costs — expenditures for nurses, pilots, dispatchers, a mechanic, maintenance, the helicopter, equipment, supplies, and administration — will make up the rest.

About 10% of these costs will be recovered through charges to patients for the helicopter service. For the balance, the hospital will draw on its other revenues.

Because of the expense and risks associated with the operation of an HEMS program, the decision to initiate a service at Duke required nearly a year of deliberation. In the end, the following considerations were paramount:

From Duke University Hospital, Durham 27710.

1. There is a clear and compelling need for responsive, reliable HEMS services in North Carolina. HEMS is a new field, and methodologies used to calculate the need for HEMS produce widely differing estimates, but it seems virtually certain that a program based in the Triangle area would make at least 300 flights per year.

2. The only existing service, which is provided when helicopters and crews are available from the Military Assistance to Safety and Traffic program at Fort Bragg, is clearly inadequate to the need and likely to reduce its services in order that military commitments can be met.

3. Duke is the kind of hospital where HEMS programs are most appropriately based. The hospital is a class I trauma center with comprehensive services in all nine trauma specialties and a wide range of critical, emergency, and intensive care services. The helicopter will extend Duke's services to patients now beyond reach, and it will bring to the hospital the very patients that our new facility is staffed and equipped to treat.

4. The operation of a HEMS program will create opportunities to expand training and research programs. Alone or in conjunction with other institutions, Duke operates thirteen different training programs in trauma, and the field is an area of growing research interest.

5. The operation of an HEMS program appears financially feasible. If cost and revenue assumptions prove accurate, the service will break even at a volume of 300 flights per year. It seems likely that the service will achieve that level of operation by the end of its first year.

6. The alternatives seem problematic at best. One is to wait for the development of a state-operated system, an idea that was first discussed in the early 1970s. In recent months there has been renewed discussion, but whether and when such a system would develop remain highly uncertain.

The other option we examined was the development of a shared service, to be operated by a new entity contracting with several hospitals. We eventually concluded that we could meet the objective of a shared service through arrangements to deliver patients to other tertiary care centers, without running the risks associated with creation and operation of a new enterprise functioning at the intersection of several hospitals.

Eventually we concluded that the hospital could and should initiate a Helicopter Emergency Medical Service, and we all look forward to the initiation of patient flights on March 1.

Duncan Yaggy, Ph.D.

North Carolina Baptist Hospital's Position

North Carolina Baptist Hospital supports the concept of a state-supported helicopter ambulance service to serve the people of North Carolina. Furthermore, when the decision is made to place such a service in the western region of North Carolina, the first such undertaking ought to be at Winston-Salem's Baptist Hospital. There are several compelling reasons for that. The hospital has the western region's only level one trauma center. It has extensive experience, in cooperation with Forsyth Memorial Hospital, in the transportation and care of high risk pregnant women. Its intensive care nursery serves all of North Carolina as well as surrounding states. Its burn unit is a vital resource for northwest North Carolina. And a significant portion of North Carolina's population lives within a short flying distance of the Bowman Gray/Baptist Hospital Medical Center.

From 300 South Hawthorne Road, Winston-Salem 27103.

Richard M. Heriot

North Carolina Memorial Hospital's Position

The North Carolina Memorial Hospital continues to support the concept of a statewide coordinated network for the provision of aeromedical transportation for patients requiring such services. The Hospital supports and endorses the recent recommendation of the Legislative Study Commission which recommends that the State of North Carolina establish such a network under the aegis of the Emergency Medical Services Division of the Department of Human Resources. It is the position of NCMH that such a public service would assure equal access to all North Carolinians. A comprehensive statewide system would also nicely link existing ground transportation, hospital emergency rooms, trauma centers and air transportation in the most cost effective manner possible. In the event that such a statewide system is not established, the North Carolina Memorial Hospital would then intend to establish its own hospital-based, aeromedical transportation capability in order to meet the unique needs of its regional burn center, neonatology center and other tertiary and educational programs which exist to serve the state of North Carolina.

From the University of North Carolina, Chapel Hill 27514.

Eric B. Munson

Editor's Note: North Carolina Memorial Hospital has hedged its bets by filing a Certificate of Need for a helicopter service with the appropriate authorities.

Vitiligo

Russell W. Eyre, M.D., Claude S. Burton, M.D., and J. Lamar Callaway, M.D.

Vitiligo comes from the Latin word vitium which means blemish. These white spots affect at least one out of every 100 people. All races are affected but the white spots are more disfiguring in darker races. Skin color is determined by the mixture of three pigments. Melanin, a complex polymer, is produced by pigment cells or melanocytes. Melanocytes are absent in the white spots of vitiligo. Two other pigments combine in the white spots to give the remaining color. Hemaglobin, a blood pigment, is red when combined with oxygen and blue after it releases oxygen to the tissues. Plants such as carrots may deposit a yellow pigment, carotene, in the skin of people who eat a lot of yellow vegetables.

A Wood's lamp, or black light, is an essential tool in the clinical evaluation of any white spot. This lamp produces ultra-violet light that enhances superficial pigment changes. The ultra-violet rays don't penetrate into the skin as far as visible light rays so superficial changes are enhanced and deeper changes are decreased. The white spots of vitiligo appear porcelain white when examined with the Wood's lamp. Another cause of white spots, tinea versicolor, which is produced by a superficial fungus infection, glows yellow in "black light." Leukoderma, or white spots, after an inflammation in the skin are usually less evident with a Wood's lamp examination. Any leukoderma should also be tested for sensation with a pin-prick to rule out leprosy.

A careful total body examination with a Wood's lamp of a patient who complains of one white spot often reveals several other less obvious spots. Exposed skin is most commonly affected, especially around the eyes, nose, and mouth. Spots are usually several inches in diameter and circular but they may grow together so that the entire skin appears bleached. The edges of the patches of vitiligo sometimes show a gradual color change from white to brown producing a three color pattern. The peak incidence occurs at 20-30 years but all ages have been affected.

The cause of vitiligo is unknown. Occasionally the onset will follow an emotional upset or the white spot may follow the course of a nerve. This leads some to believe that a substance produced by nerves is responsible for destroying the melanocytes. Vitiligo may appear after an injury or sunburn. Perhaps the immune system is exposed to parts of the melanocyte after those injuries that it usually doesn't see thus immunizing itself against the melanocyte. Other autoimmune diseases where the immune system destroys other cells are more common in patients with vitiligo. Thyroiditis, diabetes, pernicious anemia, alopecia areata, and adrenal insufficiency are all seen more commonly in patients with vitiligo. Rarely someone with malignant melanoma may present with only vitiligo. A careful history and physical examination should be done to rule out these diseases. It is not cost effective to order screening laboratory tests without some clue in the history or physical examination because although the incidence of these other autoimmune diseases is increased they are still quite rare.

Treatment is not always necessary especially if the patient is light skinned and will avoid tanning or if the spots may be easily concealed with clothing. The spots of vitiligo will burn very easily in the sun because melanin, a very effective sunscreen, is missing in them. Several excellent cosmetic products are available that provide cover-up and protection. Cover Up or Dermablend are two good products. Artificial suntan creams contain a dye, dihydroxyacetone aniline, that will stain the white spots but it is difficult to match the surrounding skin tones. A topical steroid cream has helped some patients but it isn't generally useful. If the pigment loss is extensive, permanent bleaching of the normal skin may produce the best cosmetic result. Monobenzylether of hydroquinone is applied to the skin for several months to cause complete loss of melanin.

Over three thousand years ago the ancient Egyptians discovered the most effective treatment for vitiligo. They found that when certain plants were either eaten or rubbed into the skin and the patient then exposed himself to sunlight the white spots would often disappear. These plants have high concentrations of chemicals called psoralens. Psoralens in combination with ultra-violet light can repigment over half of the patients with vitiligo. Unfortunately several years of treatment may be necessary to fully repigment someone and the treatments are not without risks. Skin cancers and cataracts are increased in patients exposed to this treatment. It is very easy to severely burn and blister the white skin with these treatments. The normal skin becomes more tanned which makes the white spots more noticeable. Despite these cautions it is the most effective and widely used treatment for vitiligo.

Drastic treatment measures are sometimes used in India, where patients with vitiligo are social outcases. Cyclophasphamide, a drug used to treat cancers, has recently been used in low doses to treat some patients with vitiligo. Most patients had a very good response. Sadly this drug has been found to cause a second malignancy, usually a leukemia, in a high percentage of those patients who have taken it. A malignancy is a high price to pay for treatment of a cosmetic problem. We hope future studies of the pigment process will reveal an effective, safe treatment for this distressing disease.

From the Division of Dermotology, Department of Medicine, Duke University Medical Center, Durham 27710.

Pervasive Procrustianism — Isopropyl Alcohol Intoxication

Ronald B. Mack, M.D.

• *Shakespeare probably didn't refer to isopropyl alcohol poisoning when he wrote, "Aye, there's the rub," but rubbing alcohol can, indeed, do you in.*

MANY medical students, some House Staff and a "rare" practitioner (surely you jest!!) would like to see diseases in neat packages — just as it says in the textbook. We more "mature" physicians realize that medicine is not quite that simple — diseases do not present in the patient exactly as the literature describes. In a similar argument, just because a patient swallows an "alcohol" in overdose you should not assume that all alcohols ingested in overdose behave and are to be treated as ethanol intoxication. The desire to make the clinical features fit the diagnosis (even if they do not) or to treat all alcohol overdoses the same (even if the alcohols are different) can be called *procrustianism*. If you persist in such thinking and cause damage to your patients thereby, you are guilty of pervasive pernicious procrustianism. What's in a name?

The condition is properly named for Procrustes. This ancient Greek was a robber of great fame and skill. He also gave new meaning to the word hospitality. It was the custom in those days to invite people to your house, including strangers, for a meal and a bed for the night. This malevolent robber tied his victims to the bed. Sad to say, Procrustes was a compulsive fellow; if the invited guest did not quite fill up the space in the assigned bed, our host would stretch the invitee until he fit the bed. If by chance the guest was too big for the bed (perish forbid), Procrustes would cut off those parts of the person required to produce a perfect fit. (Does this remind you of a hotel you once stayed at in Cleveland?)

The subject at hand today is isopropyl alcohol (AKA isopropanol) poisoning. Using the phrase "at hand" seems to be a good idea as this product is most popularly known as "rubbing alcohol." This aliphatic alcohol is used quite extensively in industry but for the average consumer it is used most commonly as a rubbing solution or as a disinfectant but also can be found in skin lotions, hair tonics, de-icing and anti-freeze products and window cleaning solutions. For home use it is typically sold in pint bottles and it possesses a distinct odor. This alcohol is not uncommonly substituted by the non-discriminating alcoholic when the good stuff is not available. You are probably more apt to be called upon to manage a patient who swallowed isopropanol accidentally or in a suicide attempt.

The absorption of isopropyl alcohol after ingestion is quite rapid, usually within one-half hour (with very large ingestions absorption may take considerably longer). This substance is distributed in body water and has a volume of distribution (V_D) about 0.58-0.70 L/kg (goody!! — could be dialyzed if the situation turns ugly). Once ingested and absorbed per the GI tract, the liver assumes control and becomes the main site of isopropanol's metabolism. The enzyme alcohol dehydrogenate metabolizes this alcohol to *acetone* (do not forget this and also please remember this does not refer to fingernail polish remover). Other ketoacids, i.e., aceto-acetic and hydrobutyric, are fortunately not produced. The end result of this enzymatic metabolism is 80% excreted as acetone and 20% excreted as unchanged. The final word on the toxicokinetics of this alcohol has not been worked out but seems to be most likely related to *first order kinetics* (the rate of transfer, i.e., metabolic breakdown, is directly proportional to the amount of the drug remaining — remember? How many times do I have to tell you that!!). Both the acetone and the unchanged isopropyl alcohol are excreted primarily in the urine.

This seems to be a good place to talk down about the dangers of *inhaling* isopropyl alcohol. For many decades (and even as we speak) this substance has been advised for the purpose of fever reduction. The literature is filled with articles on the therapeutic benefits of rubbing alcohol on the fevered patient, usually a child, in an effort to produce defervescence. I recently saw a piece of literature printed by a prominent drug company that promotes their antipyretic and also advises on the use of isopropyl alcohol "sponging." This type of anachronistic advice must cease forthwith. Strangely enough it is not the "sponging" per se that can cause intoxication because skin absorption of isopropyl alcohol does not seem to be significant. However, isopropanol vaporizes quite readily and is absorbed through the lungs with ease. Therefore, using this method of fever reduction, especially in a poorly ventilated room, can have evil consequences such as intoxication and coma. Also, it

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

has been reported recently that isopropyl alcohol has the potential to produce a chemical burn when applied to the skin of severely premature infants, e.g., when used as a disinfectant.

Just how much of this stuff can you imbibe and still live? Well, it is believed that as little as 20 ml can cause symptoms and an 8 ounce glassful is considered to be a potentially lethal dose for an adult. The toxic dose is estimated to be about *1 ml/kg* of 70% (the usual %) isopropyl alcohol. This amount produces a serum isopropanol level of 70 mg/dl. Concentrations of 50-100 mg/dl produce symptoms and levels of 150-200+ mg/dl can cause coma and death. Certainly these levels of ethanol would not usually kill; however isopropyl alcohol is different — the central nervous system depressant effects are about *twice those of ethanol* at comparable blood levels. (Is this because of the acetone produced during the metabolism of isopropanol?) Peak serum levels are reached in about one hour and any level > 50 mg/dl requires careful scrutiny by health care professionals.

It seems quite clear by now that isopropyl alcohol, because of rapid absorption, can cause adverse symptomatology quite soon after ingestion — typically within 30 minutes. The earliest complaints are apt to be gastrointestinal, manifested by pain, secondary to the gastritis and vomiting, often bloody, as well as diarrhea. The CNS seems to be hit rather decidedly from ingestion of this substance and the patient can expect to experience headache, confusion, dizziness, ataxia, stupor or deep coma. The coma produced can be quite profound and may be partially due to the formation of acetone that occurs during the metabolism of isopropanol. The thermal regulatory centers in the CNS plus peripheral vasodilatation can produce hypothermia which can be a frightening prospect indeed. If all of this was not bad enough, large ingested doses can cause myocardial depression and hypotension. The combination of *coma* and *hypotension* in a patient with isopropyl alcohol ingestion portends evil — the prognosis decreases remarkably when these two findings coexist. The pupils are typically *miotic* and this fact sometimes helps in making the differential diagnosis. Hepatic involvement can lead to hypoglycemia; a similar phenomenon occurs, not uncommonly of course, in children who ingest ethanol.

Many authorities believe that blood isopropyl alcohol levels are the best laboratory markers for the seriousness of the poisoning and gas chromatography seems to be the way to determine these levels. To help in the diagnosis it is well to remember that this alcohol imparts a distinctive odor to the patient's breath and so does the acetone and that the urine contains large amounts of ketones without glycosuria and usually without metabolic acidosis. Severe toxicity produces an anion gap greater than 12 mEq/l as well as an increase in serum osmolality. These latter two tests may be helpful in diagnosis and management when serum isopropyl alcohol levels are not readily available (and for most of us they are not immediately available). Thus if you have a patient, young or old, who is very confused or comatose, with acetonuria and without glycosuria (or hyperglycemia) who is not starving, etc. think of an acute isopropanol ingestion.

The treatment in isopropyl alcohol intoxication is somewhat tricky — there is no antidote of course and the usual poisoning supportive measures are either not useful or contraindicated. If the patient is alert and it's very early in the course, gastric emptying, via ipecac syrup, seems quite proper. In the most obtunded patient, gastric lavage is the way to go. In fact, some authors suggest intermittent or continuous lavage in such patients because isopropyl alcohol can be transported out of the blood back into the stomach. Whether to use activated charcoal or not is debatable; it is not effective in absorbing this alcohol but, on the other hand, it does no harm. Forced water diuresis does not seem to help either. It is imperative to support and maintain the vital signs which go awry in this poisoning. Ice water lavage (a Yankee trick) can be utilized to ameliorate gastric bleeding. The final question in the management of a patient severely intoxicated from isopropyl alcohol is whether or not you should institute dialysis and if so, when. This chemical would appear to be the answer to a dialyzer's dream, i.e., low plasma protein binding, low volume of distribution, etc. It appears that if you must use dialysis use hemodialysis. At present the best candidates for hemodialysis are those with hypotension not responding to simpler methods and those whose serum levels exceed 400+ mg/dl. Please bear in mind that because of this alcohol's slow metabolism the adverse clinical effects can last for two to four times those of ethanol.

By the way, be sure to drop in when you are in the neighborhood. I'm sure you would *fit in perfectly*.

Angina comes in many forms...

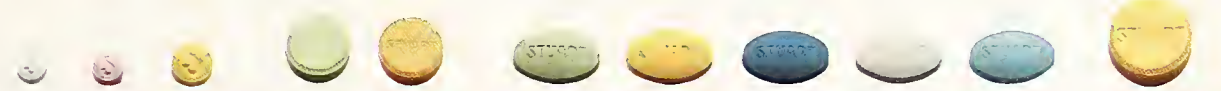


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SORBITRATE®
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Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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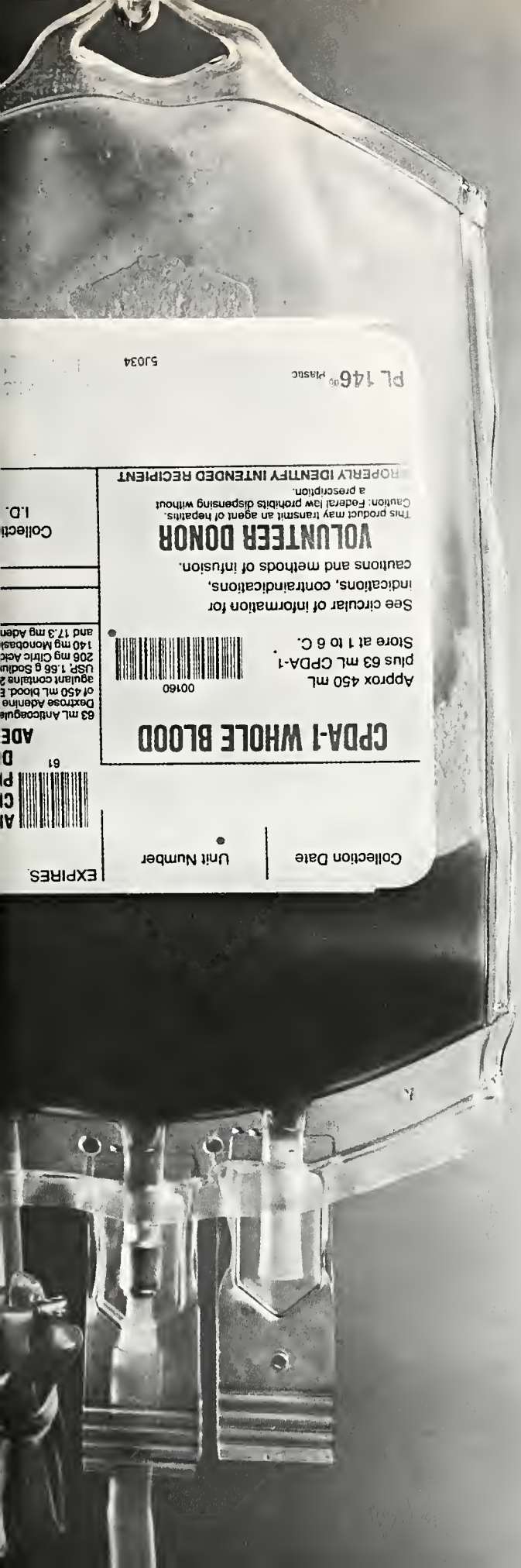


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For further information about Charter Mandala or admission procedures, contact:

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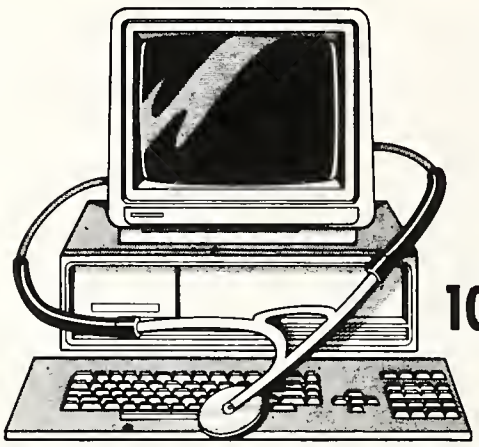


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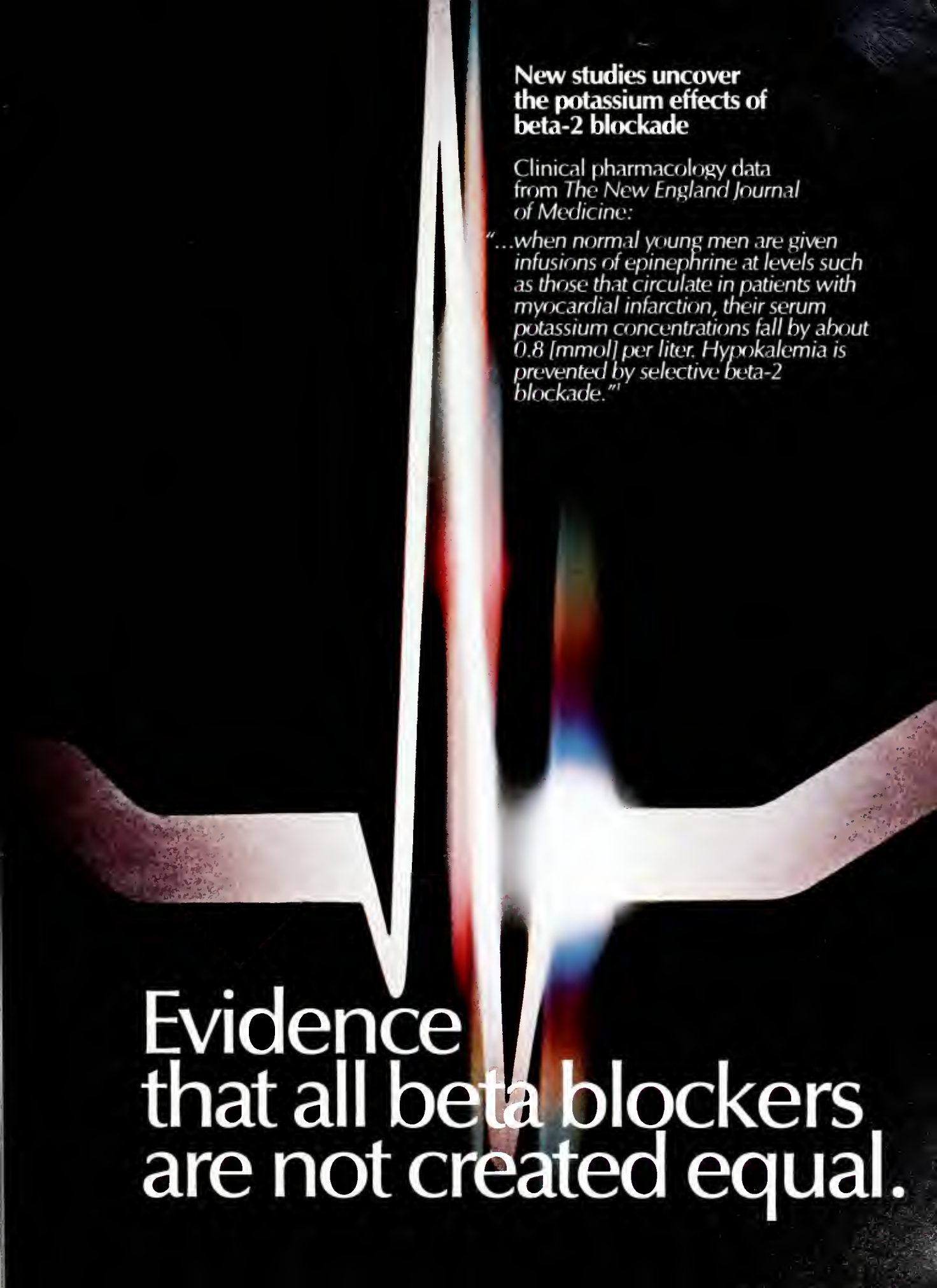
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DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia. LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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Adult Circumcision and Diabetes

Christopher M. Justis (MLS) and Edward O. Janosko, M.D.

• *Diabetes mellitus occurs significantly more often than expected in patients presenting for circumcision for balanitis and phimosis.*

THE relationship between patients requiring circumcision and diabetes mellitus has not been generally appreciated. A search of the literature reveals only two significant papers studying this relationship.[1, 2] We have been impressed with the prevalence of newly diagnosed diabetes mellitus found in patients requiring circumcision for balanitis and phimosis, and the prevalence of previously diagnosed diabetes mellitus in patients presenting for circumcision. We explored this relationship in a retrospective study of patients who underwent circumcision.

Materials and Methods

The records of 234 men ≥ 15 years old who underwent circumcision by the physicians of Greenville Urology Clinic between January 1976 and June 1984 were retrospectively reviewed; 208 of these patients had the diagnosis of phimosis, balanitis or both (table 1).

The remainder of the patients had other miscellaneous diagnoses of herpes genitalis, condyloma accuminata, carcinoma, frenular bands, congenital phimosis and others (table 2).

The presence or absence of diabetes mellitus was recorded. Patients were considered known diabetic if they were currently under a physician's care for previously diagnosed diabetes. Patients were considered new diabetics when, after they were found to have glycosuria on dip stick at our office and were subsequently referred to their physicians, they were found to have documented diabetes. The age of the patients was also recorded.

From the Section of Urology, Department of Surgery, East Carolina University School of Medicine, Greenville 27834.

Table 1

Dx. at Surgery	No. of Patients	Known Diabetics	New Diabetics	Prevalence Diabetics (%)	Prevalence New Diabetics (%)
Phimosis	90	8	2	11.11	2.22
Balanitis	82	10	3	15.85	3.65
Both	36	6	8	38.88	22.22
Total	208	24	13	17.78	6.25

Table 2

Dx. at Surgery	No. of Patients	Known Diabetics	New Diabetics	Prevalence Diabetics (%)	Prevalence New Diabetics (%)
Herpes	1	0	0	0	0
Condyloma accuminata	2	0	1	50.0	50.0
Cancer	2	0	0	0	0
Congenital phimosis	11	0	0	0	0
Penile implant	1	1	0	100.0	0
Sebaceous cyst	1	0	0	0	0
Circumcision revision	1	0	0	0	0
Frenular tear	2	0	0	0	0
Frenular band	2	0	0	0	0
Sinus tract	1	0	0	0	0
Skin graft	1	0	0	0	0
Ulcer, nonspecific etiology	1	0	0	0	0
Total	26	1	1	7.6	3.84

Table 3

Age of Patient	No. of Patients	Diabetes	Known Diabetes	New Diabetes	Prevalence Diabetes (%)	Prevalence New Diabetes (%)	Expected Prevalence Diabetes (%)*
25	75	73	2	0	2.66	0	.12
25-44	100	86	9	5	14.00	5.00	.62
45-54	24	13	5	6	45.83	25.00	1.54
55-64	17	10	6	1	41.17	5.88	3.20
64-74	11	8	3	0	27.27	0	4.71
75	7	5	0	2	28.57	28.57	4.70
Total	234	195	25	14	16.66	5.98	1.05

* U.S. National Center for Health Statistics: Characteristics of Persons With Diabetes. U.S. July 1964-June 1965 Washington, D.C.: United States Department of Health, Education, and Welfare, Public Health Service Publication, Series 10, No. 40 1967.

Results

Of the 234 patients, 39 had diabetes mellitus yielding an overall prevalence of 16.6%. Of these 39 patients, 14 were previously undiagnosed as having diabetes mellitus yielding a prevalence rate of newly diagnosed diabetes of 5.98%. It is interesting that 12 of the 14 new diabetics were diagnosed between the ages of 31 and 64.

Of the 208 patients with balanitis and/or phimosis, who comprised 88.88% of patients in the study, 37 had diabetes mellitus, an overall prevalence of 17.78% and 13 of these were newly diagnosed diabetics, a prevalence rate of 6.25% (table 1).

Table 3 summarizes the population study by age, whether diabetes was present or not, the prevalence of newly diagnosed diabetes, and the expected prevalence of diabetes mellitus in the general male population.[3]

Using Chi-Square statistical analysis, there is a significant increase in the prevalence of diabetes mellitus in all patients in our study ($p < .001$) and in patients with the diagnosis of balanitis and/or phimosis ($p < .001$), when compared by age with that expected in the general male population (see Appendix).[3]

Discussion

The dermatologic manifestations of diabetes mellitus, which are well documented, include balanitis and phimosis.[4] In 1973 Cates and Associates studied 156 patients undergoing circumcision, of whom 110 had recent phimosis.[1] Of these latter patients, 35 had diabetes mellitus and 26 of these were newly diagnosed. He concluded in his study that patients over 18 years of age with recent onset phimosis had 31% prevalence of diabetes mellitus. Later, in 1982, Chopra and Associates found a prevalence of 36.1% for diabetes in 110 patients presenting with recent onset of phimosis. In our study of 234 patients undergoing circumcision for a variety of indications, there is a significantly increased prevalence ($p < .001$) of diabetes mellitus than expected.

The majority of these circumcised patients (88.88%) presented with phimosis and/or balanitis. The prevalence of diabetes in this latter group was 17.78%, almost 17 times higher than the prevalence found in the general male population.[3]

Since our method of screening for diabetes mellitus may yield false negative results in patients who are not glycosuric at the time of presentation, our statistics represent a minimal estimate of the presence of diabetes in patients requiring circumcision. Our results confirm the studies of Cates and Chopra that a relationship exists between diabetes mellitus and balanitis and phimosis. Adult males who present with balanitis and/or phimosis should be screened for diabetes mellitus. A careful history for symptoms of diabetes and the urine dip stick for glycosuria, which can provide a reliable indication of the disease, should be the minimal office screening procedures performed.[5, 6]

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Appendix

The statistics obtained for the general reference male population were obtained from the study of 134,000 persons interviewed by the Division of Health Interview Statistics of the U.S. Census Bureau. Persons were considered diabetic if they knew they were diabetic and on the follow up detailed supplemental questionnaire were investigated as far as their diabetic history, diagnosis and medical treatment.[3]

EXCLUSIVE

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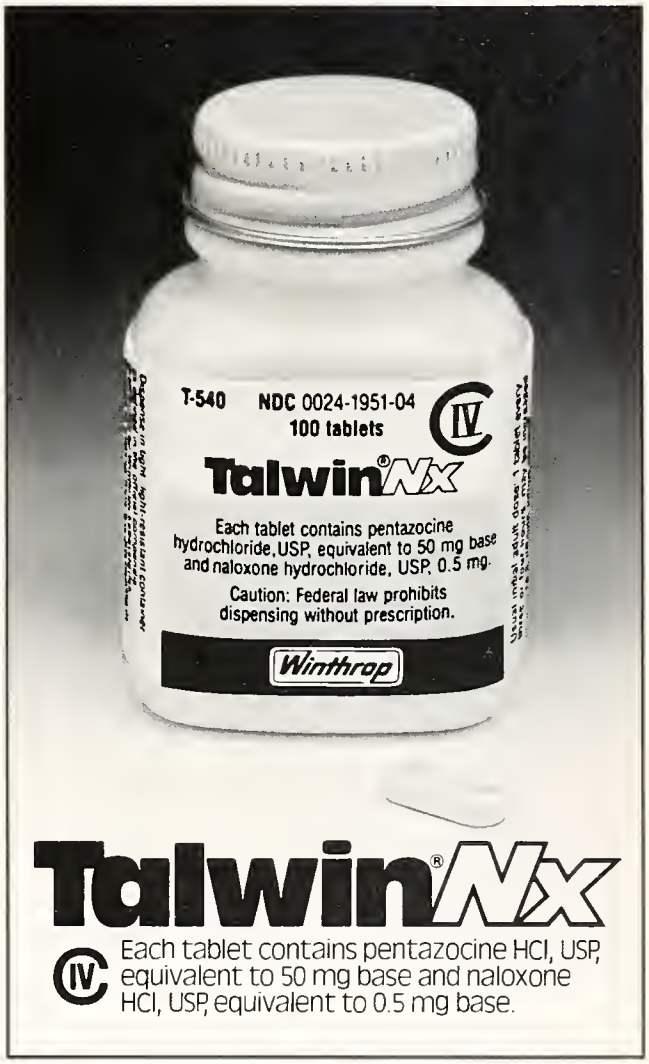
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Contraindications: Hypersensitivity to either pentazocine or naloxone

TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances. (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence.* Can cause physical and psychological dependence. (See **Drug Abuse and Dependence**.) *Head Injury and Increased Intracranial Pressure.* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Can obscure the clinical course of patients with head injuries, in such patients, use with extreme caution and only if deemed essential. *Usage with Alcohol.* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics.* Pentazocine is a mild narcotic antagonist. Withdrawal symptoms have occurred in patients previously given narcotics, including methadone. *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Precautions: *CNS Effect.* Use cautiously in patients prone to seizures; seizures have occurred though no cause and effect relationship has been established. Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours. Such patients should be very closely observed and vital signs checked; if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function.* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient. *Biliary Surgery.* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures, the clinical significance of these findings is not yet known. *Information for Patients.* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction.* Use with caution in patients with myocardial infarction who have nausea or vomiting. *Drug Interactions. Usage with Alcohol.* See **Warnings**. *Carcinogenesis, Mutagenesis, Impairment of Fertility.* No long-term studies in animals to test for carcinogenesis have been performed. *Pregnancy Category C.* Should be given to pregnant women only if clearly needed. *Labor and Delivery.* Use with caution in women delivering premature infants. Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown. *Nursing Mothers.* Caution should be exercised when administered to a nursing woman. *Pediatric Use.* Safety and effectiveness in children below the age of 12 years have not been established.

Adverse Reactions: *Cardiovascular:* Hypotension, tachycardia, syncope. *Respiratory:* Rarely, respiratory depression. *CNS. Acute CNS Manifestations.* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted. *Other CNS Effects:* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor. *Gastrointestinal:* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress. *Allergic:* Edema of the face; dermatitis, including pruritus; flushed skin, including plethora. *Ophthalmic:* Visual blurring and focusing difficulty. *Hematologic:* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other.* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance.* TALWIN Nx is a Schedule IV controlled substance.

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported. In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient. Tolerance to the analgesic effect is rarely reported; there is no long-term experience with oral use of TALWIN Nx.

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine; however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics. TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Overdosage: *Treatment.* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing.

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Delta Hepatitis — Massachusetts

AN outbreak of hepatitis B (HB) that began in September 1983 is continuing in Worcester, Massachusetts, primarily involving parenteral drug abusers (PDAs) and their sexual contacts. As of August 1, 1984, 75 cases of acute HB have been identified, 50 of which are considered outbreak-related. Fulminant hepatitis has been a prominent feature of this outbreak. Six deaths have occurred, for an outbreak-related case fatality ratio of 12%.

Patients meeting all the following criteria were considered outbreak-related HB cases: (1) an acute clinical illness compatible with HB; (2) elevated serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) two or more times greater than the upper limit of normal (when such results were available); (3) positive serology for hepatitis B surface antigen (HBsAg); (4) residence and/or primary diagnosis and treatment within the city of Worcester; and (5) a PDA or a direct contact of a PDA.

Of the 50 outbreak-related case patients, 35 were male. Twenty-nine were white, non-Hispanic; 17 were Hispanic; two were black; and two were of unknown race. Ages ranged from 15 years to 43 years (median 25 years). Forty-three patients used needles; six were sexual contacts of PDAs; and one had direct contact with open wounds of a person with hepatitis. Of the six patients who died, three were male; five were white, non-Hispanic, and one was Hispanic. Ages ranged from 19 years to 34 years of age (median 27 years). Five were PDAs, and one was a sexual contact of a known PDA.

Drugs that were self-injected were primarily heroin and cocaine. No 3,4-methylene diamphetamine (MDA), a drug implicated in fulminant HB/PDA deaths in North Carolina in 1979, was used.[1] The only potential hepatotoxin identified was alcohol.

Testing for HB markers confirmed HB in all cases. Serum specimens were available from four patients who died; three had immunoglobulin M (IgM) anti-delta virus antibodies. IgM anti-delta virus antibodies were also present in four of 22 PDAs with nonfulminant acute HB, one of seven PDA contacts with nonfulminant acute HB, and none of 11 nonoutbreak-related patients with acute HB. In addition, two of 13 non-ill HBsAg-positive PDAs had serologic markers of delta virus infection (one with IgG antibodies and one with IgM).

Editorial Note: Previous clusters of fulminant HB deaths among PDAs have been reported in this country;[1, 2] however, this is the first outbreak of fulminant HB in the United States in which the delta virus has clearly been shown to have contributed to the severity of the illness.

Delta virus is composed of a protein antigen (delta antigen) and a ribonucleic acid of low molecular weight. Although transmissible as an independent infectious agent, delta virus can only infect and cause illness in the presence of active HBV infection. To be infectious, this incomplete virus requires a coat of HBsAg.[3] Delta virus and HBV may simultaneously infect a host (coprimary infection with HBV/delta virus), or delta virus may superinfect an existing HBV carrier. Either coprimary infection or superinfection may cause acute hepatitis; both types of infection have been associated with fulminant HB in Europe.[4]

Delta virus infection is endemic in southern Italy. Based on limited serosurveys, it has also been found in the Middle East and in certain parts of South America and Western Africa. Superinfection with delta virus was implicated as the major cause of an exceptionally severe hepatitis epidemic among Venezuelan Indians in which 34 of 149 patients died.[5] Delta virus infection has been limited to hemophilia patients and PDA populations in the rest of Western Europe, North America, and Australia.[7, 8] Fulminant coprimary HBV/delta virus infections among PDAs have occurred sporadically in Los Angeles.[6]

Although delta virus is transmitted in a manner similar to HBV, to date, delta virus infection has not been reported in this country in health-care workers or male homosexuals, the other major groups at risk for HB. Because delta virus infections have never been found in the absence of infection with HBV, there appears to be little risk of spread outside of groups known to be at risk of acquiring HB. Testing for delta virus is indicated in the setting of fulminant HB infection or acute hepatitis occurring in a known HB carrier.

Control of HB outbreaks among PDAs is difficult. Efforts to control the current outbreak have focused on educating PDAs on the modes of transmission of HB and on updating physicians regarding serodiagnosis and reporting of HB and recommended prophylaxis of needle, sexual, and familial contacts of patients.[9] Since HB vaccine will prevent both HB and delta virus infections, a program to vaccinate PDAs in Worcester is currently under development as a control measure.

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Outbreak of Diarrhea Linked to Dietetic Candies — New Hampshire

A 13-year-old girl was treated at a Milford, New Hampshire, hospital emergency room April 30, 1984, for acute abdominal pain and diarrhea. Induced vomiting yielded partially digested pieces of a hard candy. The New Hampshire Poison Center notified the Epidemiology Office, New Hampshire Division of Public Health Services, that candy possibly caused the illness.

Investigation disclosed that, earlier that day, eight neighborhood playmates, ages 5-13 years (mean 9 years), had experienced abdominal cramps, urgency in defecation, and two to six loose bowel movements each, ½ to 1½ hours after eating three to 16 pieces of a dietetic candy per child. There was no known common exposure to other food, drink, or toxic substance. Only the 13-year old girl received medical attention; the other seven children recovered spontaneously within 2-3 hours after the illness began. Each of three additional playmates who ate one piece of candy and four who ate no candy did not become ill. The attack rate for children who had eaten any of the candy was 8/12 (67%); it was 8/9 (89%) for children who had eaten three or more pieces.

The candies, purchased locally, had been manufactured in Pennsylvania and are one of a number of dietetic candy products distributed widely for the past 6 years to retailers throughout the United States and to countries overseas. The candies in this outbreak each contained approximately 3 grams of sorbitol as a sweetener. Sorbitol, a hexahydric sugar alcohol, acts as an osmotic laxative. The candies were purchased in bulk and individually wrapped. The wrappers carried no ingredient information and no warning of adverse effects if eaten in excess. A survey of a number of sorbitol-containing dietetic products on the market in New Hampshire revealed instances of inadequate and inaccurate labeling.

Editorial Note: Sorbitol has been responsible for both acute and chronic diarrheal illnesses in adults and children.[1-3] In a normal adult, after a 35-gram oral dose, levels of sorbitol in blood remain undetectable, and serum glucose remains unchanged.[4] Ingestion of 10 grams of sorbitol caused bloating and flatulence in most of seven volunteers in one study. Twenty grams caused more severe symptoms of cramping and diarrhea.[5] In children, the dose of sorbitol required to produce gastrointestinal symptoms is markedly less than in adults. Sorbitol ingestion has not been associated with harmful effects other than diarrhea and gastrointestinal discomfort. In unexplained cases of acute or chronic diarrhea, a careful dietary history should be obtained, with careful attention to the possible ingestion of sorbitol.

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category 1 credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

February 17-20
Improving Residency Rotations: Curriculum Planning and Negotiations
Place: Rougemont
Credit: 20 hours Category I AMA, AAFP
Info: Dr. Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 18-20
Selected Topics for the Practicing Clinician
Place: Durham
Credit: 24 hours Category I AMA, AAFP
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 6
Eating Disorders of Childhood and Adolescence
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

March 7-9
Diving Accident Management and Hyperbaric Oxygen Treatment
Place: Durham
Credit: 20 hours Category 1 AMA; 2.0 CEU
Fee: $280
Info: Cindi Easterling, Box 3108 DUMC, Durham 27710. 919/684-6878

March 20
Pulmonary Embolism — Acute Care and Prevention
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

April 13
Neurosciences Update
Place: New Bern
Info: William B. Hunt, Jr., M.D., Box 2157, New Bern 28560. 919/633-8607

April 15-June 7
Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category 1 AMA per week
Info: James F. Martin, M.D., Center for Medical Ultrasound, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4505

April 17
The Back — From Thoracic to Sacral
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

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Place: Asheville
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May 1
The Pregnant Therapist
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-3571

OUT OF STATE

February 16-23
Radiology Postgraduate Course
Place: Ixtapa, Mexico
Credit: 25 hours Category I AMA
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February 24-28
Duke Aging Symposium
Place: Palm Beach Gardens, FL
Credit: 15 hours Category 1 AMA
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March 4-7
Interventional Techniques and Radiologic Management of the Emergency Patient
Place: Williamsburg, VA
Fee: $425
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 16
Reconstructive Plastic Surgery
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Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

March 29-31
Ophthalmology: Cataract Surgery and Intraocular Lenses
Place: Williamsburg, VA
Fee: $275
Info: Kay Parrott, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 12-14
Third Annual Symposia on Anesthesia for Ambulatory Surgery
Place: Williamsburg, VA
Fee: $250
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 19-21
Seventh Annual Conference on Emergency Medicine for the Primary Care Physician
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-27
Twentieth Annual Pediatric Springfest
Place: Williamsburg, VA
Fee: $235
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-28
Annual Meeting, Virginia Society of Otolaryngology-Head and Neck Surgery
Place: Irvington, VA
Info: Donna Strawderman, 4205 Dover Road, Richmond, VA 23221. 804/353-2721

May 3-5
Fifth Annual Clinical Concerns in Primary Care
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

May 10-12
Fifth Annual Radiation Oncology Course
Place: Williamsburg, VA
Fee: $275
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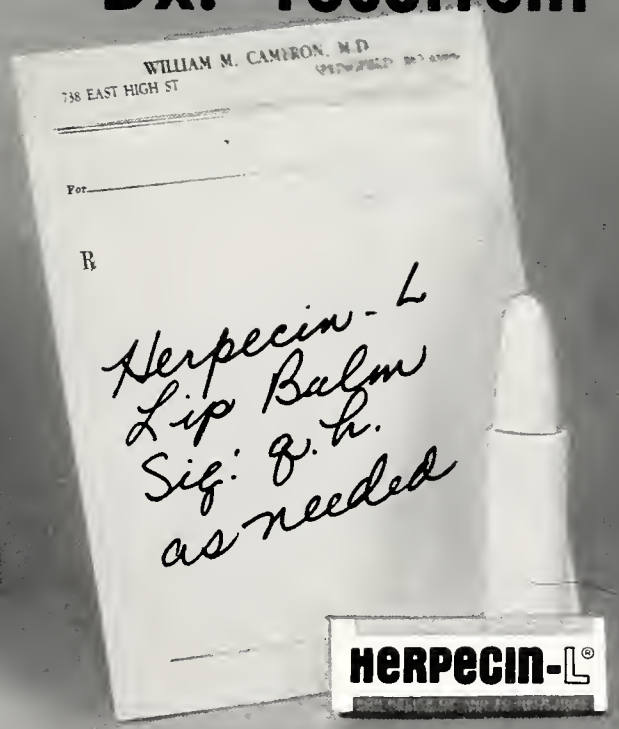
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Letters to the Editor

The following letter was accompanied by a photocopy of the St. Paul Medical Services Division advertisement from page 777 of the December NCMJ.

To the Editor:

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H. W. Johnson, M.D.
5305-G Wrightsville Avenue
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Panic Disorder

To the Editor:

Dr. Burch's editorial on hypoglycemia[1] is an excellent review of this popular but uncommon disorder and the challenge presented by patients whose complaints suggest this syndrome. The differential diagnosis of patients with symptoms of adrenergic discharge is exhaustive and well known. One of the more recent additions to this list, however, seems to be frequently overlooked by specialists and primary care physicians alike: panic disorder. This psychiatric term for a predominantly biological process is a handle that often fits, and is (best of all) readily responsive to treatment. The following case is a typical one.

A 31-year-old female nurse was referred to the ECU Med/Psych Clinic for evaluation of "shaking spells." For the previous two years she had experienced frequent discrete episodes of various symptoms, including diaphoresis, tremor, nausea, fatigue, weakness, headache, dry mouth, blurred vision, and anxiety. While these episodes were not consistently related to food intake, she nonetheless felt strongly that she was suffering from fluctuations in her blood sugar, and had been evaluated by at least two endocrinologists as well as several other physicians. Physical exams, numerous blood glucose determinations, several glucose tolerance tests, various serum chemistries, and thyroid function tests had all failed to demonstrate any disorder of glucose metabolism or other evident disease. She had also been seen periodically by a psychologist for help in dealing with some situational problems, but had noticed no change in her symptoms during these times.

Panic disorder is defined[2] as an anxiety state manifested by panic attacks ("discrete periods of apprehension and fear" with physical symptoms of adrenergic excess) which occur spontaneously and without apparent precipitants (such as physical exertion, exposure to danger or phobic objects, underlying medical or psychiatric disorders, and the like). It is not uncommon, affecting perhaps 1 to 3% of the population, and occurs most often in young to middle-aged females. While distinct from the agitated distress which frequently results from ruminative worrying ("crescendo anxiety"), spontaneous panic attacks can often result in a secondary or anticipatory anxiety in which the patient avoids those places and situations associated with previous attacks. The pathophysiology for panic disorder is still undefined, although a recent model[3] suggests that changes in intraneuronal pH and lactate levels underlie the physical symptomatology. Drug therapy with tricyclic antidepressants or monoamine oxidase inhibitors usually results in a rapid and marked improvement, as does treatment with alprazolam (Xanax), a triazolo-benzodiazepine with both anti-anxiety and anti-depressant effects.

Since this patient met the criteria for panic disorder, the nature of this syndrome and the possibility that it was her diagnosis were fully discussed with her. Physical exam, serum chemistries, and an overnight dexamethasone suppression test were all within normal limits. Alprazolam, which she had taken on occasion at a bedtime dose of 0.5 mg for sleep, was increased to 1.0 mg t.i.d., and within 10 days her symptoms had abated. She has been maintained on a lower dose for several months without recurrence.

She continues to occasionally see her psychologist for assistance in dealing with the other stresses in her life.

James G. Peden, Jr., M.D.
East Carolina University School of Medicine
Greenville 27834-4354

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Education vs Training

To the Editor:

I think your editorial, "Training Is No Substitute for Education" (NCMJ 1984;40:579-80), was timely and pertinent. It is a message that somebody should remind us of from time to time.

J. Stuart Gaul, Jr., M.D.
1900 Randolph Road
Charlotte 28235

Creation vs. Evolution

To the Editor:

In the August 1984 issue of the *North Carolina Medical Journal* there was an editorial entitled "A View from the National Academy of Sciences: Science and Creationism." This was almost entirely a quotation from Dr. Frank Press as he wrote the preface to a booklet entitled *Science and Creationism* that was written to be distributed by the National Academy of Sciences. After reviewing the edito-

rial I waited through the September, October, and November issues for some response to the statements Dr. Press made. This wait has been in vain as there apparently has been no response or at least none that has thus far found its way into the *North Carolina Medical Journal.*

Since I realize that an evolutionist may experience a dangerous rise in his blood pressure when someone points out the grossly unscientific nature of the evolutionary theory, I hestitated to respond to Dr. Press. However, in the long run I yielded to the urge to take a chance with the blood pressure problem knowing that we can usually treat this particular situation successfully. How I wish the muddled reasoning of the pseudoscientist who believes in evolution could be dealt with as easily.

Dr. Press did not at any time address the essential and all-important question of our origin in the preface to the booklet *Science and Creationism.* Instead just as in the title that the National Academy of Sciences has chosen for the booklet, the statements he made would have one believe the evolutionary theory is a proven fact and that the theory of creation is unscientific. Such is far from the actual truth. Dr. Press says, "Most important, the scientific method requires that the fact-seekers remain open-minded, are willing to accept changes indicated by the signposts of evidence." I could not agree more. However, I have been amazed for years that the evolutionists generally refuse to examine the facts in an open-minded way. If we are to gain anything from examining the theory of evolution as compared to the creationists' theory of our origin, our examination must be ruled by the accepted scientific observations that pertain to the origins of the human species. Fortunately for our discussion there are plenty of facts to peruse.

On the other hand, Dr. Press says, "The theory of evolution has successfully withstood the tests of science many, many times." This is untrue since the evolutionary theory would crumble instantly when compared with the known facts of science.

What are the tests of science? Since Dr. Press does not mention them, allow me to list some of the more important. First, in discussing the origin of species, have we ever seen a single new species develop from a previous species? The answer is in the negative. Which theory does this fact support? Obviously it supports the creation theory.

Secondly, do we have any scientifically acceptable documentation of human life on this planet beyond 10,000 years ago? Again we must give a negative answer, and again we must admit that there being no earlier fossils of humans prior to this rather short length of time, the evolutionary theory again diminishes in scientific importance. It should even be mentioned that some unscrupulous evolutionists in their zeal to supply scientific proof to the theory of evolution have manufactured gigantic hoaxes to prove scientifically their theory when they cannot find support for it otherwise.

Thirdly, does the early existence of animal life many thousands of years ago prove or support the theory of evolution of man from lower animals? Obviously, it does not unless some type of bridge between the two is also evident. There being no evidence of such a bridge the mere existence of animal life a million years ago does not bear at all on a theory of evolution of the human species.

Finally, what does the fact that evolutionists will not respond to the above questions and similar facts relative to our origin say about the strength of their scientific basis? Obviously when one side of a supposedly scientific discussion will not address the observable facts as Dr. Press has recommended, it certainly denegrates his stand in the eyes of the scientific world. We should watch very carefully and see which side of the debate accepts the observable facts open-mindedly and which side does not. Evolutionists constantly seek to persuade and convince by prejudice and deceit. Such can never be considered as scientific evidence.

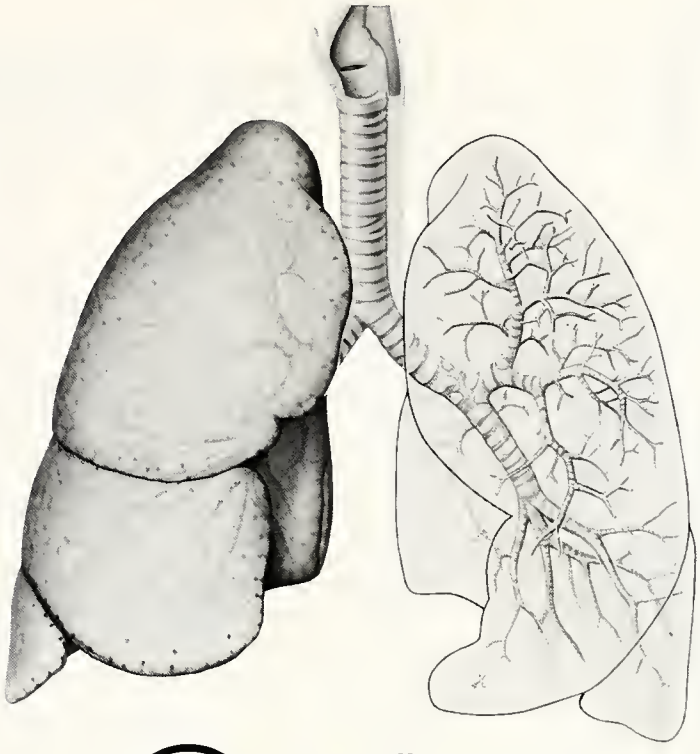
Dr. Press points out the fact that we once thought the world was flat. Also at one time the majority of people looked upon earth as the center of everything, when now we know the earth is not even the center of our little solar system. Consensus changes but truth does not.

Other things regarding science could be said, and I for one applaud any effort of science to examine this issue in a scientific way. If purely scientific views had been used to examine our origin, there would not be much to talk about now. Unfortunately the theories of origins are involved, like it or not, with one's understanding of God. Since this is true, preconceptions have been and continue to be very influential in everyone's considerations regarding how man arrived here. Dr. Press recognized this fact when he said that acceptance of the evolutionary theory does not alter the religious principles of many religious leaders. I must agree with Dr. Press on that statement. However, I will remind you that even though we have many excellent religious leaders, it was the religious leaders who led the crusades, held the inquisitions, allowed pogroms in many areas, and caused our Lord to be crucified. This debate is hardly a place to appeal to support from "religious leaders." Instead I believe that only scientific evidence should be admissible.

The truth is that despite the various similarities between man and lower animals, we have certain irreconcilable differences. Dr. Michael DeBakey recently pointed out the major biological species barrier between man and animals in discussing the transplantation of animal hearts into man. Man and animals have no common ancestry. The greatest of these differences is not our chromosome count or adult physiognomy which of course is enough to disprove the theory of evolution to the true scientist with an open mind. The difference of which I speak is the matter of the eternal soul. This subject is the only consideration I know where consensus favors the creationists, because most people believe man is a spirit who possesses an eternal soul. This is very strong among Jews and Christians and has been shown by many surveys to be a majority opinion in this country. Only the creationist has a reasonable explanation for this as the evolutionist is generally convinced that man is simply a higher animal and has no intrinsic spiritual difference from lower animals. If one wishes to deny humankind's eternal considerations and overlook the many scientific facts of the matter of man's origin, then and only then can he take the ultimate in scientific hypocrisy and support the incredible theory of evolution.

Marion W. Griffin, M.D.
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Brief Summary Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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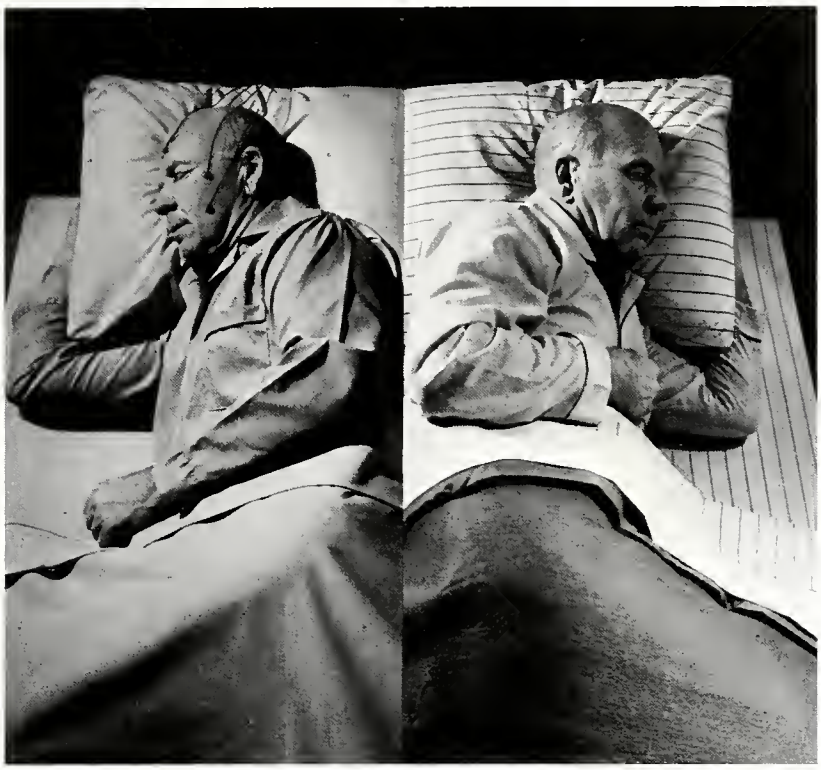
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Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

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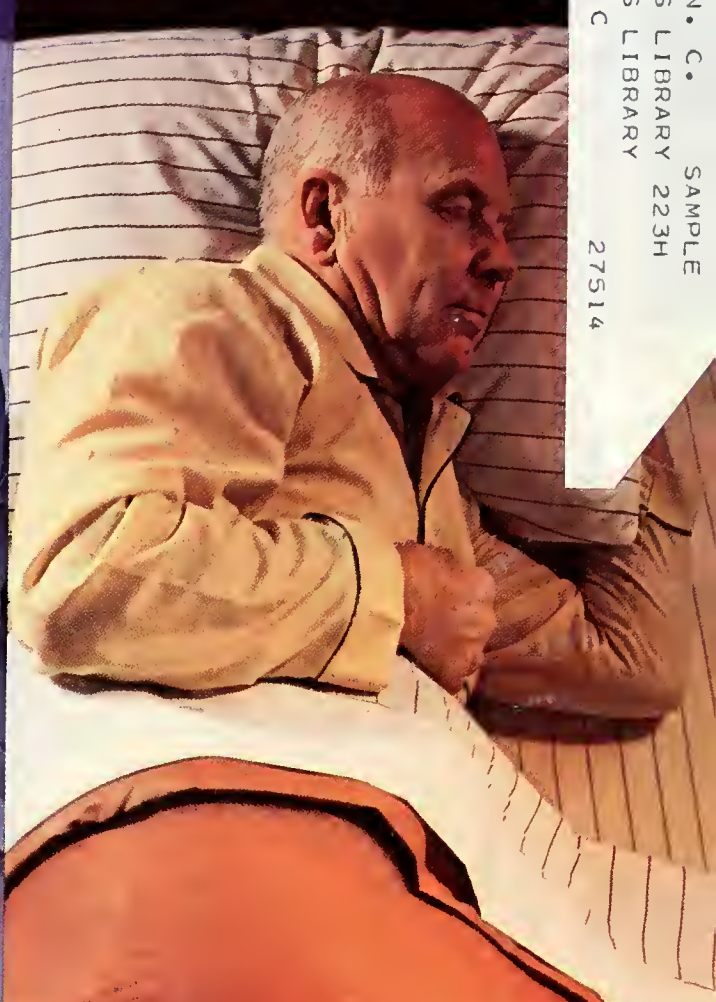
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Good Grief Makes Good Sense, by J. Trig Brown, M.D.

Grieving the demise of a loved one is a normal reaction which helps us to adapt to our loss, as illustrated below in a Thomas Bewick woodcut over 150 years old. page 153



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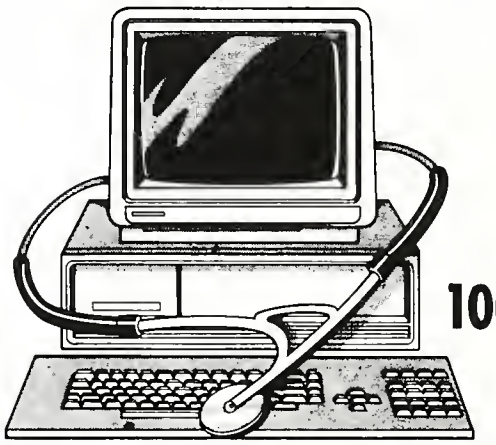
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SPECIAL ARTICLE

Medical Economics, Ethics, and Education: Some Old Wines in New Bottles

Milton W. Hamolsky, M.D.

I am honored by your invitation to serve as your Sergei Zlinkoff Visiting Professor for 1984. I participated, as a medical resident under Dr. Hermann Blumgart at the Beth Israel Hospital in Boston, in the medical care of Mr. Zlinkoff when he was referred from New York for further study and attempted management of his complex, difficult, and unresolved medical problems. His private physician was Dr. Mack Lipkin, unknown to me but described by Dr. Blumgart as the "finest practicing internist" he knew. We failed to make any substantive contribution to Dr. Lipkin's understanding or plan of management for Mr. Zlinkoff. I learned more, and probably for the first time, about the realities of "the art" of medicine and the limitations of "the science" of medicine from Dr. Lipkin who became, and has remained, my prototypic role model of the knowledgeable, experienced, wise, and caring patient's doctor and teacher of students. Despite, but also partly because of, our frustrations, Mr. Zlinkoff willed a large sum of money — in tribute to Dr. Lipkin — for the creation of a Foundation for Medical Research and Education. Two years ago, the Board of Trustees of that Foundation — again in tribute to Dr. Lipkin — created five Visiting Professorships to foster the principles exemplified by Mack at five medical centers where Dr. Lipkin had made his unique mark. I am proud but humbled by this opportunity to add my personal and professional tribute to Dr. Mack Lipkin.

When I received your invitation, visions of sweeping and profound and statesmanlike pronouncements on the great issues of Medicine flitted kaleidoscopically through my mind. At last — the opportunity to address to a captive audience such problems as the Growing Crisis in Medicine; the Decline of the Physician in Society; the Impact of the Scientific and Technological Explosions on the Humanism of Medicine; the Science versus the Art of Medicine; Specialization, Fragmentation, Non-accessibility within the Medical Care System; the Soaring Costs of Medical Care and the Demands by Government, Business, Insurers, and the Public to Contain Costs while Assuring High Quality of Care for Every Citizen; the Rising Roles of the Government, the Consumer, Third Party Payors and an Avalanche of Alphabetized Regulatory Agencies; the Law and Ethics and Politics in Abortion, Death with Dignity, Research on Humans, Do Not Resuscitate Policies, Allocation of Limited Resources, Rationing of Health Care, Medicine's Share of the GNP, etc. — ad infinitum, ad absurdum, and ad boredom. And then, as is the special privilege of the outside consultant, to leave town before you have figured out what he really said.

My surging "ego," however, was flattened by my more realistic "id" — for I do not consider myself particularly qualified to bring to this medical center any unique insights which have not already been offered profusely by Medicine's more qualified statesmen. I would be more comfortable sharing with you some experiences in my personal intellectual hobby of Endocrinology — and the thyroid in particular. But that is not, in my understanding, the purpose of the Zlinkoff Professorship. I have chosen, therefore, to offer some personal reflections on biases based on the experiences I have been privileged to enjoy as a clinician, teacher, one-time academic researcher, and administrator of sorts.

A favorite ploy of the lecturer to reawaken his audience is to quote some trenchant pronouncement and then emphasize its timeless relevance by revealing that it was written in, say, 1895. Let me offer such a quotation:

"My basic thesis is that the fundamental strength of medicine has been, is now, and will always be the one-to-one highly personalized relationship of a patient and his/her doctor — the individual human being in pain or anxiety or fear and the chosen doctor dedicated to cure the disease if possible, if not . . . to alleviate the pain or suffering and, in any event, to share and ease the discomfort of body and mind. When all the smoke of rhetoric has cleared — of politics and economics and philosophy — and when the threatening promise of the computer has reached its equilibrium — that interpersonal relationship will remain the final common pathway of the nobility of medicine. And I submit that it is the slippage of that noble tradition which is the root of most societal disaffection, of the malpractice crisis, of the increasing interpositions of others between the patient and the doctor, of the growing threat of governmental interventions, of the underlying unease of the patient and the doctor in our society."

Those sentiments, articulated frequently by many, were offered by me just seven years ago in an address to one of the first graduating classes of the new Brown Medical School. I believed them deeply. I want to believe them now. But I wonder about the recent forecast by the physician chairman of the American Hospital Association Council on Physicians. "I see," he states, "only two kinds of doctors surviving (in the future) — those who are affiliated

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with alternative provider systems and those who are directly affiliated as hospital staff physicians. This means the end of the voluntary medical staff as we know it. Hospitals will no longer be able to afford (sic!) the individual solo practitioner who has no vested interest in the preservation of hospital resources through cost-effective medical care and is unlikely to control a sufficient volume of admissions to have the leverage over hospital administration that they have had in the past." I have difficulty grasping any substantive link in that bleak outlook to the Care of a Patient concept of Francis Peabody or Hermann Blumgart.

To retain some semblance of my ingrained concept of Medical Grand Rounds, I would begin with the case history of Mrs. A. G. — a 78-year-old housewife, mother of three children, who entered our hospital because of her second — or perhaps third — stroke. She was unresponsive on entry and bits of her history were garnered from a daughter, her recently engaged rheumatologist, and her hospital record.

Mrs. G. was characterized in her early years as a strong, active, intelligent, self-sufficient wife and mother, who had been for the last few years in her usual state of chronic, debilitating, deforming arthritis for which she was receiving Prednisone but caring for her progressively senile and incapacitated 82-year old husband, despite one or two strokes which had left her with residual left-sided weakness and some slurring of speech.

She also had hypertension and was on two antihypertensive agents, adult onset diabetes mellitus, moderately well-controlled by an oral antidiabetic agent, a history of angina pectoris with, possibly, one major ischemic episode two years previously, mild congestive failure treated by digitoxin and Lasix, and mild azotemia (serum creatinine of 2.8). She was also taking Elavil because of some depression over the past one to two years.

Evaluation in our Emergency Department revealed a comatose patient responding only to painful stimuli, blood pressure of 180/112, pulse of 118, 32 respirations, and temperature of 102°, left-sided paresis, and right-sided paralysis, slight neck stiffness, distended neck veins, bilateral basilar rales, 2+ peripheral edema, multiple premature beats (by EKG, multifocal ventricular contractions), depressed reflexes with a positive Babinski reflex on the right, unequal pupils, nonpalpable arterial pulses distal to the femorals. Studies revealed an elevated WBC with a shift to the left, mild anemia, blood sugar of 283 with 2+ acetonuria and 2+ proteinuria, serum creatinine of 3.6, normal electrolytes except for a serum potassium of 3.1, mild hypoxemia with CO_2 retention. Normal values were obtained for the sedimentation rate, prothrombin time, partial thromboplastin time, uric acid, serum bilirubin, serum calcium, and phosphorus, total protein and A/G ratio, SGOT, LDH, creatinine kinase, serum amylase and alkaline phosphatase. EKG revealed Q waves in leads 2, 3, and AVF. Chest x-ray revealed an enlarged heart with bilateral congestion and a questionable area of beginning consolidation in the right lower lobe. A CAT scan was unrevealing except for moderate cerebral atrophy; EEG revealed a diffuse metabolic encephalopathy. Lumbar puncture revealed elevated pressure and protein and 450 red cells per mm.[3]

She was treated with oxygen, Lasix, Ampicillin, regular insulin, hydrocortisone and a slow I.V. drip for keep-open purposes. Shortly after entry, she developed ventricular tachycardia which responded ultimately to Procainamide but was followed by hypotension which responded to Dopamine. Because of progressive CO_2 retention, she was intubated and transferred to the Intensive Care Unit. Despite all measures, she remained comatose but was sustained on a respirator, monitor, and I.V. hydration. Several runs of ventricular tachycardia were managed pharmacologically. Her EEG deteriorated but continued to show scattered, sporadic spikes. The neurologist declared her status as essentially irreversible.

After ten days on the Intensive Care Unit, her ventricular ectopy gradually subsided, her blood sugar, electrolytes and blood gases were normalized, her blood pressure was controlled at 150/94, her creatinine stabilized at 3.2, a urinary E. coli infection and her presumed pneumonitis responded to antibiotics and she was transferred to the Medical Ward, essentially stable but comatose.

The resident and nursing staffs continued their exemplary clinical care. One daughter requested that "everything possible be done for mother." Another daughter and son revealed that mother had once stated, "If I ever become like poppa, please do not let them keep me alive with all those tubes." Her rheumatologist, the physician-of-record, had only recently undertaken her care, for her old family doctor had died. He advised continuation of all therapies, was unwilling to write a DNR order but advised that, if she failed, a "slow-code" should be carried out. The Utilization Review Committee advised the physician that she had received the maximum allowable hospital care and attempts were undertaken to transfer her to a long-term care facility. The DRG monitor advised us that Mrs. G. had passed into the "outlier" group. After 47 days, her blood pressure dropped progressively despite Dopamine, and she expired.

Her hospital bill was $73,000.

What can we learn from such an experience? I would offer some selective personal reflections — under the rubrics of economics, ethics, and education.

A growing body of anecdotal experiences, retrospective data, and ominous projections indicate that the problems of Mrs. G. will increasingly dominate the medical scene. The progressive aging of our population is now a given — much of it the inevitable result of the advances in medical science, technology, and public health. Our future is enveloped in the constellation of chronically dependent patients; higher costs; the schizophrenia of the health care planners in sober and detached objectivity versus the family and patient in the Emergency Department and Intensive Care Units who want the very best — now; the political platitudes of one class, high quality care for all versus the hard, increasingly dominant finality of those who pay and, therefore, call the tune; the cool rationality of the — uninvolved — philosophers, humanists, and ethicists except when they or family are patients; the lonely physician torn between his primary obligation to his patient versus his societal responsibilities to the larger community.

The litany of medical economics is impressively persuasive. Rising hospital costs, increasingly expensive technologies, ancillary services, drugs, long-delayed improve-

ments in salaries of health care personnel, the general economic stagnation and inflation of the 70s, over-supply of hospital beds, the putative physicians' glut, escalating annual costs for business of employees' health benefits, a tottering Medicare system threatening an already endangered Social Security system, etc., have contributed to the oft-repeated — and increasingly accepted — dogma that society has decided that Medicine's 10 to 10.5 percent share of the GNP is "enough." In the economists' view, according to Fuchs, 1) resources are scarce relative to wants, 2) these resources have alternative uses, and 3) people have different wants and assign different values to them. The economists' problem is how to allocate resources optimally to meet health needs. And so we have spawned prospective rate setting, certificates of need, maxicaps, zero budgeting, reallocation of resources (euphemism for whose ox gets gored), Health Planning Councils, a national center for technology assessment (which lasted only three years), increasingly raucous debates over "competition" versus "regulation," HMOs, PSROs (now PROs), DRGs, redesigned benefit packages (copayments and deductibles), pre-admission certification, utilization review, mandatory ambulatory surgery, mandatory second opinions, home care programs, use of alternative delivery systems, preferred provider agreements, the "prudent-buyer" concept, health care coalitions, for-profit health care systems, hospice programs.

Somehow, the case of Mrs. G. is overwhelmed by this statistical deluge. Yet it is symbolic. Can Medicine justify the growing thousands of Mrs. G.'s and the do-everything-we-can approach for all? To what end?

I am impressed that there is "fat" in the system. Every serious attempt to validate the use of lab tests and ancillary diagnostic procedures results in a 20% reduction — at least while the supervision persists. Various prepayment plans do appear to result in significantly lower hospitalization rates. The growing challenge to the "do everything we can" approach to the Mrs. G.'s is valid and gaining adherents. I am concerned, however, over the growing power and dominance of the "cost containment" component of the equation. I believe that Medicine's greatest challenge in this sphere is to effect a more realistic balance of the usually coupled — but usually submerged — component of the quality of care. It is far easier to calculate costs, to dominate with impressive charts and graphs. Although we profess to know quality, we have failed to present our case with comparably impelling force. We have failed to define reasonable limits, we offer insufficient countervailing quantitative economics of the values and quality of the life we prolong, the technologies we offer, the benefit component of the cost/benefit ratio. Pioneering efforts are now being made — chiefly by the newly evolving Divisions of Primary Care or General Internal Medicine. They merit our strong and sustained support. For we must be constant participants in the ongoing dialogues of allocation of health-care resources, and we must have data and reasonable plans and feasible operations. Otherwise our past platforms of medical research and medical education will be undernourished and the result will be an inevitable deterioration of the health care we will be able to provide.

Some personal examples come to mind. I believe that when I was a resident I, too, would have "done everything" for Mrs. G. For I knew that it was not my privilege to play God; I knew that failure to do everything I could bordered on the unacceptable euthanasia; I was more comfortable in doing something rather than the more ego-threatening, carefully valued, selective procrastination; it was easier to impose my previously nurtured dedication to treat, to cure, to save than to grapple with the bothersome considerations of family members or — even more unsettling — the vaguely indistinct or clear, but suspect, intimations of the dying patient. But now, after 30 years of personal experiences (most of which were unique lessons which, somehow, did not solve the next one) and learning from the changing values and expectations of our society from the pronouncements of the humanists, economists, ethicists, and politicians, I am not so sure. I am now more prepared to stay my hand — to explore the patients' preferences, to adjust to the families' concerns (for I have learned that many — perhaps most — families are grateful to the physician who will open and lead the discussion of alternatives, alleviating their guilt to be the initiators).

In a recent two-week period, I counted eight articles in the *New York Times* on "Many See Mercy in Ending Empty Lives," "The Courage to Talk About Death," "French Doctors Admit Helping Patients Die," "A Person Owns Himself," "The Struggle to Save a Life Already Lost," "Declaration on Euthanasia of the Vatican," "Bureaucracy Should Not Intrude," "One-Sided Dialogues (the Failure of Physicians to Discuss the Issues of CPR with Patients and Their Families)."

I am not significantly more certain of what is *the* right course in so many cases of Mrs. G., but I am more secure in my responsibility to consider assuring comfort and accepting DNR and, if that is the careful consensus, to write the explicit orders and the explanatory progress note, to withhold the respirator, feeding gastrostomy, cardiac pacemaker, to do without the sedimentation rate, serum bilirubin, multiple blood gases and electrolytes, alkaline phosphatase.

Another personal reflection — as chief of a Department of Medicine, I receive from our administration a monthly, computerized print-out of the performance of each member of our medical staff — compared with our hospital-wide averages — listing each individual patient of the physician, his DRG classification, the length of stay, use (and cost) of x-rays, lab tests and other ancillaries and, most pointedly, the total cost of the stay to the hospital compared with the DRG-Medicare reimbursement. Despite my determination not to be carried along, I find myself focussing on "the losers" as compared with "the winners." I do not know what the ultimate impact — local or Federal — will be, but I am uneasy. I have heard of two orthopedists in another hospital whose staff reappointments were denied because their lengths of stay for hip and back cases were 21% above the median of other staff orthopedists. Their suit is now in the courts. I have heard rumors of modification or elimination of the reimbursement for medical education costs of residents and fellows. And I am uneasy.

I reflect also on the inordinate costs of malpractice insurance. Impressed by the general thrust for fair and equitable settlements in cases under the Workmen's Compensation

Act in our community as compared with the a priori imposition of an adversary battle to prove malpractice by someone or anyone when a patient has suffered an adverse or unexpected outcome, I suggested to our Medical Society and legislative representatives creation of a new system fashioned after the Workmen's Compensation mechanism. I was commended for my civic zeal and then gently squelched for my naivete with the admonition that 92% of the State legislators are lawyers. "Do you really think," I was asked, "that they will ever vote for such a change?"

There is another paradox of medical economics, less honorable in its ethical implications but increasingly more real in my experience. Society, or its spokespersons, proclaims its preference for the "good old family doctor type of M.D."; its vocal spokespersons decry the lack of preventive medicine, holistic care, and the generalist. But society's mechanisms for reimbursement deny the resultant logical resource allocation. Society pays well for the hospitalized patient, for surgical procedures, for the specialist with his invasive technologies, for the performance of all kinds of lab testing. But it does not recognize the physician who spends the extra time to communicate more fully with his patient and family, society will not stop smoking, nor wear seat belts, nor consume less alcohol, nor reduce overweight, will not reimburse appropriately for many elements of ambulatory or preventive care. Quality physicians on my staff have convinced me that they are sensitive to the importance of, and need to, communicate more fully with their patients, but that they are frustrated by economic necessities to compromise, that there has been a steady erosion of the personal and professional fulfillments of being a doctor, that there is, simply, not as much fun in being a doctor. Virtually every intern on my staff is deeply in debt when he starts, facing three to five or six more years of training, and then — at age 30 — will face a significant startup cost of building a practice, accelerating malpractice insurance premiums, the looming glut of physicians, difficulties in obtaining staff membership, the realization (as others) of children to educate and the chilling fact that his postponed economic security depends largely on his continuing health and ability to see patients. Since physicians are also human beings, it is unrealistic to ignore the conflicting pressures of society's expectations (and the good physicians' preference) for effective and time-consuming communications on the one hand but a distorted reimbursement system on the other which preferentially rewards hospitalization, acute care, invasive technology, "doing rather than thinking and discussing."

I have the uneasy sense that it may already be too late to slow, to modulate the rapidly accelerating juggernaut of the "economic facts of life" which daily dominate our local scene and loom threateningly more decisive on the national scene.

The power of the purse is casting a lengthening and enveloping shadow over the doctor's traditional prime obligation to his patient, insinuating its determinative role upon our ethical standards of professional conduct. I received two weeks ago the Ethics Manual of the American College of Physicians, reprinted from two 1984 issues of the *Annals of Internal Medicine*. The table of contents lists some 36 topics such as the Physician-Patient Relationship, Financial Arrangements, Informed Consent, Conflicts of Interest, Sharing Fees, The Incompetent Colleague, Advertising, Obligations of the Physician to Society, the Relationship of the Physician to Government, to the News Media, to other Health Professionals, Commercialization of Medicine, Physician Unions and Strikes by Physicians, Resource Allocation, Medicine and the Law and, finally, Patient Autonomy, Quality of Life, Care of the Hopelessly Ill. As I read the sections, my thoughts returned to Mrs. G. who symbolizes the awesome dilemmas created by the capacity of modern biomedical technology to prolong and sustain key physiological functions, for indeterminate periods, in patients in vegetative or comatose states balanced uncertainly against increasing public awareness of Medicine's technological virtuosities but prognostic uncertainties, financial and emotional drains on patients and families, emerging patients' rights and patient autonomy and newly evolving concepts of the quality of the sustained biological existence in terms of sentient or cognitive functional potential. Mrs. G. nags at me as I read increasing empirical and retrospective data that the terminally ill receive proportionately much more expensive medical care than other patients, that over 20 percent of all nonpsychiatric hospital and nursing home expenditures are spent on the care of the terminally ill, that although only five percent of all Medicare enrollees died in 1967 and 1968, 22 percent of all reimbursements from that program were made on their behalf, that the cost of care of non-survivors of cancer or intensive care units is roughly twice that of survivors, that intensive care costs seem to be inversely related to the probability of patient survival. Mrs. G. looms before me when I am advised that efforts directed at reducing cost and increasing efficiency must be focused on such high-risk, high-cost, low-yield groups. Yet I am impressed by one cautioning study of intensive care patients that found that "among non-survivors, the highest charges were due to caring for patients who were perceived at the time of admission as having the greatest chance of recovery and among survivors, the highest charges were incurred by those thought to have the least chance of recovery," i.e., patients with unexpected outcomes — death or survival — incurred the greatest costs. The study concludes that "simple cost-saving solutions, such as withholding resources from the hopelessly ill, are difficult to apply to an individual patient because prognosis is uncertain." I am not very comforted by the reassurance of one hospital's Optimum Care Committee that "economic considerations must never serve as the *sole* criterion for disposition of patients." I worry about a vague feeling of the dwindling sanctity of life, so precious a fundament of our profession in the face of the insidious interpolations of cost containment. And yet I struggle to justify my ultimate personal decision to permit and to help Mrs. G. to die with dignity as my primary ethical obligation to do what is best for Mrs. G., unswayed by diverting considerations of economics. Mrs. G. thus symbolizes what I believe will be a growing problem for the caring physician — epitomized elliptically by the conflicting construct of economics versus ethics.

What, then, is the balancing role of medical education? I do not have to certify the glorious accomplishments of science and medicine, the legacy of relief and comfort

provided to billions of people on this planet, the primacy of basic scientific knowledge as the lasting foundation of our profession. Somewhere between 1910 and 1912 in this country, it is stated, a random patient with a random disease consulting a doctor chosen at random had for the first time in the history of mankind a better than 50-50 chance of profiting from the encounter. But, we are told, the science of medicine has so dominated our profession that we have come to neglect the patient as a person. The patient, it is said, knows how he feels but doesn't know what he's got, while the doctor knows what he's got but doesn't know how he feels. The milk of human kindness has been curdled by molecular biology. And so the cry is raised from all quarters for a return to "humanistic medicine" — to me a logically redundant tautology. A concept has grown that there is somehow an inherent contradiction between science and humanity, between technology and compassion.

And so we talk of the art of medicine — the unique application of our scientific knowledge and clinical skills toward our primary responsibility to strive to understand the individual human being for the maintenance of health or the amelioration of disease. And we extol the artist in medicine who weaves into his fabric elements of history, religion, sociology, anthropology, psychology, music, art, and literature. There is an important caveat against the growing tendency of some — under the guise of humanistic compassion — to become impatient with the demanding and difficult and everchanging complexities of biochemistry and molecular biology and the hard, long-term attainment of clinical expertise. For compassion and empathy and sharing will not suffice if the physician does not determine that the situational depression of the recent widow is due *this* time to mild hypothyroidism which, once suspected, can be readily diagnosed and cured for a few pennies a day; if he is not alert to the possibility by minimal neurologic changes that the recent migraine headaches which have always, as now, occurred under stress signal *this* time a brain tumor; if he fails to palpate, on *this* visit, an enlarged spleen which might uncover an emerging leukemia in his tired and run-down, always complaining, neurotic housewife or businessman.

I mentioned previously the nostalgic longing for the "good old family doc." I believe that people do not really want the old family doctor with his limited therapeutic armamentarium but are expressing a preference for the doctor who "will take care of me as an individual, who knows (because he cares) about my family background and past history and me as a person, who will listen to me, talk to me, explain to me, give me the knowledge and opportunity to share in my decision-making and health care and not just send me around for a lot of blood tests and x-rays. But he should also know the latest and the best in diagnosis and therapy, or be ready to obtain the best for me when I'm really sick — but still remain the responsible integrator of my total overall care."

As in the schizophrenic praise and blame of science and technology for the blessings and evils for mankind, there is a swelling tide of criticism of medical education for most or all of the decline of humanistic medicine in the modern age. Out of the cascade of papers, lectures, seminars, curriculum committees, task forces and commissions, I have discerned among the pathogenetic mechanisms catalogued 1) a basic genetic imprinting on the RNA and DNA of the doctor-to-be, 2) any or all features of the educational systems before medical school, 3) fundamental changes in society from the basic religious, moral and ethical values of humanitarian and societal concerns to the secular goals of permissiveness, relative affluence, self-fulfillment and personal happiness, 4) the grinding competitiveness to get into medical school, 5) the hypocritical selection process which urges a liberal education in the humanities, social sciences, and arts, but awards the cherished admission largely to science majors with high scholastic grades and skills in mastering the multiple-choice regurgitation of memorized facts, 6) the hardening process of professionalization upon the idealistic medical student who learns to "go along" in order to "get along" in the system, 7) perversion of the medical faculty whose primary role should be to teach but whose reward system is the research productivity priority of the promotion committee, 8) the irresistible pressures toward specialization by peer cloning and economic inequities.

This past month the Association of American Medical Colleges published a pamphlet — *Physicians for the Twenty-First Century* — the conclusions, recommendations, and observations of the Panel created in 1981 on the General Professional Education of the Physician (GPEP) and College Preparation for Medicine. It is a most impressive document, representing the distillation of the thinking and work of representatives of 96 U.S. and Canadian medical schools, colleges, and universities, and professional societies of Medicine. Based on the assumption that all physicians, regardless of specialty, require a common foundation of knowledge, skills, values, and attitudes, it offers five major conclusions, 4-6 specific recommendations relevant for each, the observations leading to the conclusions, an epilogue of Other Important Considerations, an afterword and appendices.

In the Introduction, the Chairman writes, "The medical course cannot produce a physician. It can only provide the opportunities for a student to secure an elementary knowledge of the medical sciences and their applications to health problems, a training in the methods and spirit of scientific inquiry, and the inspiration and point of view which come from association with those who are devoting themselves to education, research, and practice. Medicine must be learned by the student, for only a fraction of it can be taught by the faculty. The latter makes the essential contributions of guidance, inspiration, and leadership in learning. The student and the teacher, not the curriculum, are crucial elements in the educational program." Ironically and somewhat wistfully, this quotation is from the report of a Commission on Medical Education of the Association of American Medical Colleges submitted 52 years previously, in 1932. "Plus ca change. . . . "

It is not possible to encompass with any brevity the sweeping, scholarly, and trenchant pronouncements of this GPEP Report. I recommend its careful study.

I have learned in Medicine, however, that when we are grappling with multiple pathogenetic mechanisms for any disease, it usually means that 1) we do not know the actual mechanism(s), 2) it is difficult to devise a rational therapy,

and 3) if our efforts appear to help, we cannot define any responsible cause-and-effect. But, as in all human endeavor, lack of understanding elicits flexible vocabulary, and so we have "idiopathic" or "multifactorial."

I would offer some personal reflections on certain factors in medical education which have impressed me.

Until our genetic probes can pinpoint the chromosomal loci for empathy and compassion, I believe it is possible to teach and to learn those elements subserved by the phrase "humanistic medicine." I have been impressed by the idealism of medical students and later of interns, and by the selfless and humane behavior of many hard-working, dedicated practicing or full-time physicians. I believe I have seen multiple examples of major alterations in sensitivity to, and caring for, people — usually attributable in my judgment to the examples of respected role models. I know — when I reflect — the important shaping of whatever I have become by Dr. and Professor Hermann Blumgart, by Dr. Mack Lipkin, by my chief resident, by my nurse — wife — and by my uncle — an L.M.D. in a small, western Massachusetts town. It is dismaying, therefore, to read the critical assessment by sociologists who followed a class of 80 students from the admission process over three years at McMaster School of Medicine during its determined and massive efforts to correct the cited faults of medical education. They conclude that the progressive loss of idealism of the medical student is not a temporary diversion but rather is inherent in the very demands of professionalization. In their need to strive for competence and passage, students turn off their emotional reactions; psychosocial issues are relegated to secondary importance. They perceive instead the medical profession's expectations of affective neutrality toward patients. The authors describe the loss of idealism in the context of a symbolic moral drama wherein professionalization is seen as a process of differentiation and alienation from lay society and of elevation to a position of detachment and control. The neuropeptides of my gastrointestinal tract rebel against those of my cerebrum but the challenge is clear.

At a more simplistic level, I am critical of the traditional system which greets the student on entry to medical school who comes with an idealism based largely on the anticipation of helping sick or troubled people and, instead, proscribes any meaningful contacts for the eager novitiate with patients for two years, insisting instead on the passive memorization of bones, the brachial plexus, cranial nerves, the Krebs cycle, E. coli, the Fick principle — with a rare, grudging intimation that somehow, some day, it will help the survivors deal with human ills. Is there any wonder that the third year has been viewed as liberation from irrelevant science and, with stethoscope draped insouciantly around his neck, the student is a pushover for the clinician who says "never mind that biochemical junk you had. I'll show you the real stuff." I have seen the intellectual excitement first aroused when the student sees a 23-year-old mother of two who is going blind, relentlessly, from her diabetes because we do not know how to prevent or reverse it and then hungers for the first time to learn carbohydrate metabolism, insulin action, glucagon, membrane permeability, sorbitol. I have seen the interactive excitement of a clinico-pharmacologic or clinico-physiologic session obliterating by the focus on a human patient the artificial barriers between detached basic sciences and clinical relevance by shuttling back and forth around the patient in the same time-frame. I have seen the medical student pursuing in enraptured detail the pathology, biochemistry, physiology, immunology, and psychosociology of his puzzling patient with cirrhosis of the liver. I have shared the maturing efforts of the student when he is first challenged to understand both the disease — the deviation from normal — and the illness, the sum total of the effects of multiple complex factors on his unique human being. I have seen his hurt when he first learns of our limitations in ultimate understanding of most problems, his discomfort when he must make decisions with inadequate data, his pain when he must face suffering he cannot alleviate, or the inevitable failure — to his conditioned psyche — of the death of his patient. These are the essence of medical education — and they require a more appropriate balance of nurturing of the clinical relevance of our scientific knowledge.

Such sentiments have been enunciated more elegantly, eloquently, and forcefully by Professor Neame, a senior lecturer in human physiology at the University of Newcastle in Australia in the September 1984 issue of the *Journal of Medical Education,* supplemented by an accompanying editorial by Dr. Cavazos, a member of its editorial board. Professor Neame presents, in spare and forceful analyses, the most unrelenting, powerful criticism of the non-integration, indeed anti-integration, of basic science to any clinical relevance of the current system of medical school education, defines sharply more proper goals and objectives and offers specific remedies. I urge all of us involved in and troubled by the medical education of our future physicians to read and ponder and react to his landmark contribution.

My experiences lead me to urge the restructuring of our system to elevate the stature, participation, and respect of the experienced, knowledgeable and caring clinician to the a priori guaranteed status of the white-coated, specialized, full-time, research oriented assistant professor.

I hasten to defend myself against the inevitable, reflex attack on such an anti-academic stance. No one respects more than I do the overwhelming values of research, the attainment of peer approval by obtaining competitive grant support, broadening service on National Committees and Advisory Councils, sharpening of critical capacities by service on editorial boards. No one accepts with any more certainty than I do the fundamental and essential contributions of the dedicated army of researchers — basic scientists and clinical investigators — whose collective contributions are responsible for the current and unlimited future status and potential of our noble profession.

But I have learned that all skilled researchers are not a priori effective teachers of medical students. I ask only for a more equitable balance.

One important element of this balanced restructuring relates to the incentive and reward systems for our medical faculties on the campus and in the hospital. Over the years I have heard the pronouncements of the power structure extolling the essential role of teaching and the good clinical teacher in the medical school. But I have been frustrated — as a student when we lost our two best teachers because, we

were told, they had not published enough; as a resident when our best practicing clinicians were replaced as Visits by the newest subspecialists, skilled in their restricted spheres but impatient and uncomfortable when challenged by more general problems of our patients; and as a Professor and Chief of a Medical Service when the decisions of our Promotions Committee appeared to take the teaching commitments and skills of our staff faculty for granted, and assigned higher and sometimes final determinative priority to the bulk of publications, or success in obtaining research grants.

My plea again is not for the slightest diminution of the stature of, and sustained support for, the research scientist or research-oriented clinician. I am unreservedly committed to increased and sustained support for basic science and clinical investigation and I decry the short-sighted, short-term vagaries and constrictions of society's support for research. In the context of this discussion, I emphasize the need to upgrade the recognition of and support for the clinical teacher, whether private practitioner or full-time academician, if we really mean what we say about the all-important values of clinical teaching.

In this context also I am increasingly impressed by the fundamental contributions — in the continuing total care of patients, in teaching these relevant basic values, in extending the parameters of research studies — of the newly emerging General Internal Medicine faculty, both those committed to a "full-time" academic career and those practicing generalists finding a welcoming home for their talents and commitments. They are proving their worth and they represent, if properly nurtured, a promising additional strength for the shifting spectrum of Medicine.

In closing, as I reflect upon these remarks, I believe they may serve as the real essence of this attempted tribute to Dr. Mack Lipkin.

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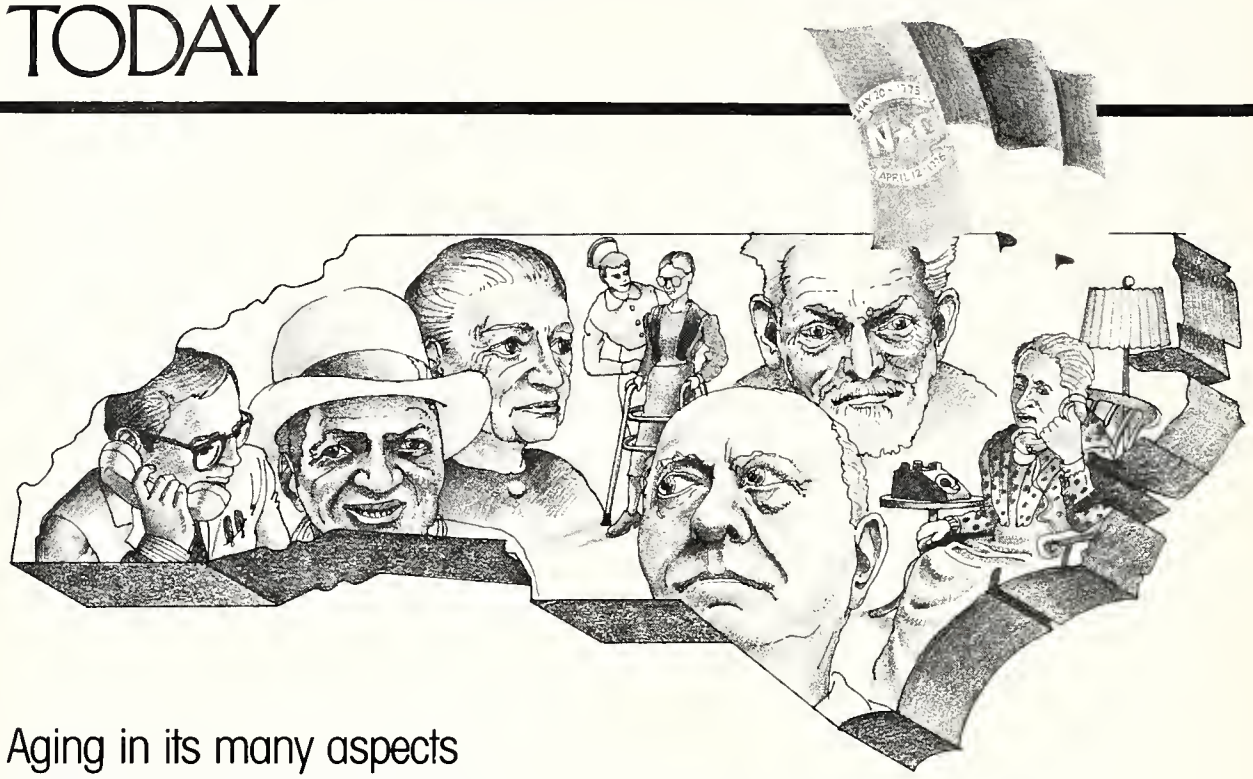
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NORTH CAROLINA MEDICINE TODAY



Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

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*Feighner JP, *et al. Psychopharmacology* 61:217-225, Mar 22, 1979.

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.
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Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.
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SCIENTIFIC ARTICLE

Blood Replacement for Repeat Cesarean Section: "Type and Screen" Preferable to Cross Matching

David H. Chestnut, M.D.

Introduction

THE safety and efficacy of the type and screen in obstetric practice have been previously reported.[1-3] Time-honored practice patterns are slow to change, however; it is the author's observation that physicians commonly continue to request cross-matching of two units of blood for patients scheduled for repeat cesarean section. It is the purpose of this communication to report recent experience with blood replacement for patients undergoing repeat cesarean section in a university hospital.

Materials and Methods

The hospital records of all patients undergoing repeat cesarean section at Duke University Medical Center between November 1, 1981, and April 30, 1984, were retrospectively reviewed. Patients transfused preoperatively were excluded from the study.

Each patient chart was manually reviewed for collection of maternal parameters. Socioeconomic status was defined according to whether the patient was a private or a staff (resident physician) patient.

Results

Between November 1, 1981, and April 30, 1984, 218 patients underwent a repeat cesarean section at Duke University Medical Center. Five anemic patients were excluded from the study because they were transfused preoperatively. Table 1 includes maternal characteristics of the remaining 213 patients.

Eight of 213 patients underwent repeat cesarean after an unsuccessful trial of labor; an additional 61 patients were in early labor and/or had spontaneous rupture of membranes prior to repeat cesarean. The remaining 144 patients underwent elective repeat cesarean. Table 2 includes details of operative management.

Four patients (1.9%) were transfused intraoperatively. One patient with a placenta previa underwent emergency hysterectomy for intractable bleeding secondary to placenta accreta; this patient was transfused four units of blood intraoperatively and an additional three units postoperatively. The remaining three patients were transfused two units of blood intraoperatively; hemodynamic instability was not an indication for transfusion in these three patients.

Two patients were each transfused two units of blood within the first 24 postoperative hours. Thus six of 213 patients (2.8%) were transfused perioperatively.

An additional 11 patients were transfused after the first 24 postoperative hours but prior to discharge. These 11 patients received a total of 27 units of blood.

Ten of 213 patients had a preoperative hematocrit less than 30. Five of these ten patients were transfused either intraoperatively or postoperatively.

Mean hematocrit prior to discharge was 32.1. Mean postoperative hospital stay was 5.3 days.

Discussion

Reisner recently reported experience with blood replace-

Table 1
Maternal Characteristics

Number of patients	213	
Mean age	25.3	
Race: White	58	(27.2%)
Black	150	(70.4%)
Other	5	(2.3%)
Socioeconomic status: Private	50	(23.5%)
Staff	163	(76.5%)
Mean weight in pounds	168.2	
Mean weeks gestation	38.3	
Mean preoperative hematocrit	35.6	

Table 2
Operative Management

Anesthesia: General	108	(50.7%)
Epidural	103	(48.4%)
Spinal	2	(0.9%)
Uterine incision: Low transverse	209	(98.1%)
Vertical	4	(1.9%)
Tubal ligation	101	(47.4%)
Mean operative time in hours*	0.96	

* Excluding one patient undergoing cesarean hysterectomy; operative time for this patient was 2.7 hours.

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ment during repeat cesarean; one of 148 patients (0.7%) was transfused intraoperatively.[4] He did not report the socioeconomic status of the patient population or the incidence of postoperative transfusion. The data presented herein confirm a low incidence of perioperative transfusion in patients of primarily lower socioeconomic status undergoing a repeat cesarean section in a teaching hospital.

Had two units of blood been crossmatched for all 213 patients in this study, the perioperative crossmatch:transfusion ratio would have been 29.7, considerably higher than the recommended ratio of 2.1 to 2.7.[5] Routine preoperative crossmatching of two units of blood necessitates setting aside blood for a large number of patients who will not require transfusion. Such practice not only is time consuming for blood bank personnel, but also depletes the supply of reserved units for patients with more critical needs for transfusion. Crossmatched blood may exceed its expiration date without being utilized, and larger inventories are required.

The type and screen has been previously reported as a safe and efficacious alternative in obstetric practice.[1-3] Blood bank personnel initially determine the patient's ABO group and Rh factor. Patient serum is subsequently mixed with reagent red blood cells from two donors in order to screen for the presence of red blood cell antibodies. Unexpected antibodies are noted in 0.7 to 3.5% of patients;[1, 3, 6] compatible blood is then crossmatched preoperatively for these patients with a positive antibody screen.

If the antibody screen is negative, the blood bank technologist verifies that a reasonable quantity of ABO group- and Rh type-specific blood is available for transfusion. Should blood be urgently needed intraoperatively for the patient with a negative antibody screen, a 15 second saline spin using the patient's serum and donor red cells is performed to avoid transfusing incompatible blood secondary to clerical error. If the need for transfusion is less urgent, a crossmatch, utilizing both incubation of low ionic strength solution and an antiglobulin test, can be completed within 20 minutes. In one study of 23,857 patients, only 0.06% of patients had antibodies identified at the time of the crossmatch that had not been noted with the initial antibody screen, and most of these antibodies were thought to be insignificant during transfusion.[6] Thus the type and screen has been reported to be 99.99% effective in preventing the transfusion of incompatible blood.[7]

It is not surprising that utilization of the type and screen results in significant financial savings for the patient. At this medical center, the patient charge for a type and crossmatching of two units of blood is greater than three times the patient charge for a type and screen.

The committee on standards of the American Association of Blood Banks has stated that "guidelines for preoperative blood orders . . . should be based on local surgical transfusion utilization patterns, and must allow for modification for selected patients."[8] The presence of preoperative anemia, placenta previa, or coagulopathy may therefore prompt the physician to request a full crossmatch prior to performing repeat cesarean.[4, 9] The data presented herein, however, suggest that the type and screen deserves greater utilization by North Carolina physicians prior to performance of repeat cesarean section.

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INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years; in clinical trials with Norlestrin 2.5/50 involving 96,388 cycles, there was a pregnancy rate of 0.22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See WARNING No. 5)
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved.

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy. Birth Defects in Offspring and Malignancy in Female Offspring.* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected: (a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage; hypertension, gallbladder disease; benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Norlestrin [21] 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [21] 2.5/50 is available in compacts each containing 21 tablets. Each tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [Fe] 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [FE] 2.5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [28] 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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EDITORIAL

Blood Replacement for Repeat Cesarean Section

Roy T. Parker, M.D.

SINCE World War II, the maternal mortality in North Carolina has been reduced from an average of 200 per 100,000 live births in the years 1945-1950 to 10 per 100,000 live births in the years 1976-1980. The maternal mortality rate is still three-fold higher in black women than in white, indicating a major influence of social, educational, and economic factors. Hemorrhage, hypertension (induced or aggravated by pregnancy) and infection were the primary major causes of maternal death. Hemorrhage is still a significant problem, but death from bleeding is of a different etiology than the classic abruptio placenta, placenta previa and postpartum atony of 40 years ago. The so-called "minor causes of bleeding" such as induced abortion, ectopic and intravascular coagulopathy are more prominent now that the death rate has been reduced primarily in the major causes. Nonetheless, there is no substitute for blood component therapy in acute blood loss and shock. Recognizing the vital influence of improved socioeconomic and educational factors and general medical care upon the decline of maternal mortality, the major advances in obstetric practice and obstetric facilities have been the *sine qua non* of saving the lives of mothers and babies. In 1945 there were fewer than 50 certified obstetricians and gynecologists in North Carolina and today there are more than 550. Equally striking is the fact that in North Carolina in 1945, greater than 50% of deliveries were in the home, whereas today over 98% are in hospitals. With regard to safety for mother and baby, *hospital delivery is a singular important factor*. The knowledge and skill to transfuse blood for obstetric hemorrhage in a hospital setting is a life-saving measure that cannot be challenged.

During this same interval since World War II, there has been an explosion of medical knowledge, research, and patient services that has made the U.S.A. the envy of the world, and North Carolina has shared fully in most of these medical advances. The results have been an inordinate increase in the number of physicians and hospitals, both federally sponsored, and without much regard for consequences. Medicine, through education, research and patient services, has created the nation's third largest industry, the cost of which is approaching $200 billion annually. The counterreaction now underway is to reduce physician output by 15%, to close smaller underutilized hospitals, to limit patient services, and to economize in patient care. This means that each and every hospital unit must seek ways to function effectively with less expenditure.

Elsewhere in this issue, Dr. Chestnut has presented a clinical study that demonstrates a means of reducing cost in the blood transfusion service for obstetric patients undergoing cesarean section, without compromising the safety of mother and baby. The average blood loss associated with a cesarean section is about one liter (twice that of a vaginal delivery), and not uncommonly it is greater. Therefore, the time honored practice to request cross-match of two units of blood for cesarean delivery is not without reason. Further, bleeding during delivery is most likely to be fatal to the mother when whole blood or blood components are not immediately available. The question is, can the "type and screen" provide the safety without the added cost of "type and crossmatch" and setting aside of two units of blood?

Of 213 patients who had repeat cesarean delivery in the Duke Medical Center between November 1, 1981 and April 30, 1984 and were eligible for review, four (1.9%) were transfused intraoperatively, and two additional patients were transfused within 24 hours, to equal 6 patients (2.8%) in the immediate perioperative phase of care. Thus, 207 patients and 414 bottles of blood would have been typed and cross-matched and set aside that were not needed in the "on demand" emergency situation.

The "type and screen" methodology is described and includes patient's ABO group, Rh factor, and red blood cell antibodies. Dr. Chestnut points out that unexpected antibodies are noted in 0.7 to 3.5% of patients and in such patients, compatible blood is cross matched preoperatively. For the remainder of patients, where an uncomplicated cesarean section is expected, the blood bank verifies that "a reasonable quantity of ABO group- and Rh type-specific blood is available for transfusion." Next, Chestnut reports that "should blood be urgently needed intraoperatively for the patient with a negative antibody screen, a 15-second saline spin, using the patient's serum and donor red cells, is performed to avoid transfusing incompatible blood secondary to clerical error. If the need for transfusion is less urgent, a crossmatch, utilizing both incubation of low ionic strength solution and an antiglobulin test, can be completed in 20 minutes." His study and literature reports (including large numbers of patients) show that the "type and screen" technique is 99.99% effective in preventing incompatible blood transfusions.

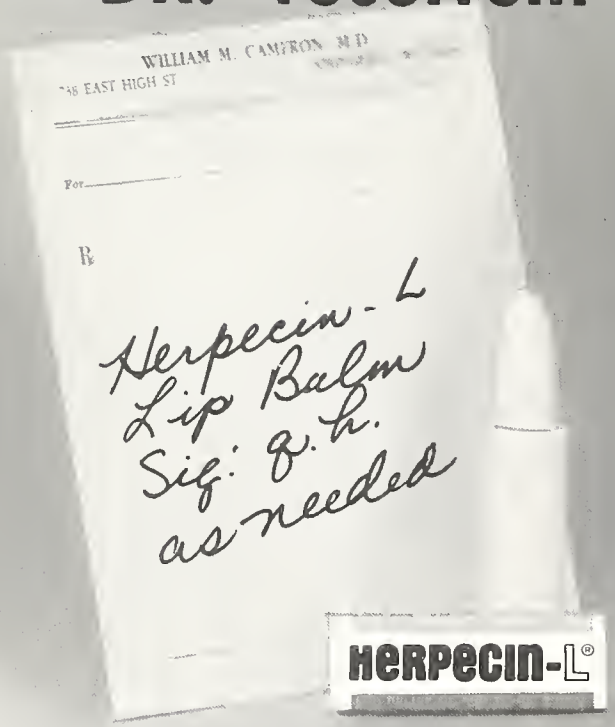
Dr. Chestnut's final admonition is that patients who have pre-existing conditions such as "anemia, placenta previa, or coagulopathy may therefore prompt the physician to

From the Department of Obstetrics and Gynecology, Duke University Medical Center, Durham 27710.

request a full crossmatch prior to performing repeat cesarean.''

The ''type and screen'' methodology as described in this study and carried out in the Department of Obstetrics and Gynecology in the Duke Medical Center is safe for repeat cesareans and primary cesareans in healthy patients who do not have associated anemia or bleeding problems, provided that there is strict adherence to the outlined technique and the admonitions. My only concern is that other ''shortcuts'' will negate the experience gained during the past 40 years in preventing death from hemorrhage in obstetric patients.

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EDITORIAL

Physicians Can and Should Offer Direction for the 1985 Legislature

Harold R. Silberman, M.D.

UNTIL recently, one issue that politically polarized many people has been how or whether religion should mix with government. Even on the Sunday before the General Assembly opened, some of our state legislators heard still another "sermon" on "Mixing Religion and Politics," this one by Dr. William H. Willimon speaking in Duke University's Chapel. Today, a much more urgent mixture should concern our profession . . . medicine and politics. In that interface, many questions are being raised. Are we being told how to practice? Is current and impending Federal legislation creating two classes of patients? Who is guiding government, at any level, toward implementing those regulations that help protect the interests of our patients and the health of all citizens?

Current newspapers focus on many significant issues confronting the 1985 General Assembly beginning with which political party has the real power and proceeding to Governor Jim Martin's 443.5 million dollar tax-cut proposal, while moving through a dozen other topics as diverse as highway priority, child pornography, phosphates in laundry detergent and gubernatorial succession.

Doctors have opinions on some or all of those matters to be sure. But major concerns of our North Carolina Medical Society will be addressed this session as well. In 1985, your Society plans to pursue and support legislation pertaining to: medical cost containment; preservation of local health departments; medical malpractice; allied health professionals; and traffic safety. It hopes to enhance motor vehicle safety in four specific areas: first, by a requirement that seat belts be used by everyone at all times; second, by urging re-enactment of G.S. 20-137.1, a bill that deals with compulsory application of child passenger restraint systems; third, by lobbying for a requirement to have both public land permits as well as age restrictions in order to engage in motor-cross racing; and fourth, by achieving immunity from any legal liabilities for those doctors who choose to report impaired drivers to the Division of Motor Vehicles.

Because physicians are trained to detect both physical and mental disabilities that could affect the ability of a person to operate a motor vehicle, they have sometimes been impotent witnesses to the beginnings of what will result in vehicular loss of life or serious injury. By current North Carolina statute, there is no obligation to report anything. There is always the moral duty, and recently, as in the Tarasoff case, *a responsibility* to *warn*, as neurologists will in the case of patients with seizure disorders. In that situation, most go beyond reminding their patients about the risks of operating an automobile and suggest reporting voluntarily their problem to the Department of Motor Vehicles. Almost always a note to that effect is written into the chart. But what about those patients who default after appropriate instruction? Then too, consider a much more frequent disease than epilepsy, namely chronic alcoholism. There the ethical question has two parts — should we report someone and to whom?

The North Carolina Medical Society wishes to establish a mechanism for reporting and to remove the stimulus not to report because of some fiduciary or confidential relationship existing between patients and their doctor. In May 1984, via direction from the Medical Society's Committee on Traffic Safety and through a recommendation from its Committee on Legislation, the Executive Council presented to the House of Delegates Report X: "RESOLVED, the North Carolina Medical Society recognizes the cost to society of allowing impaired drivers to operate motor vehicles and seeks legislation permitting physicians to report impaired drivers to the appropriate state officials and providing physicians making such a report with immunity from any and all liability." Your House of Delegates resoundly passed that resolution. Dr. H. David Bruton and his Committee on Legislation are now helping to draft a proposition which will be sponsored and brought to the General Assembly this spring. Of four different pieces of legislation in the area of motor vehicle safety, this is the only one that will be drafted and introduced by the Medical Society.

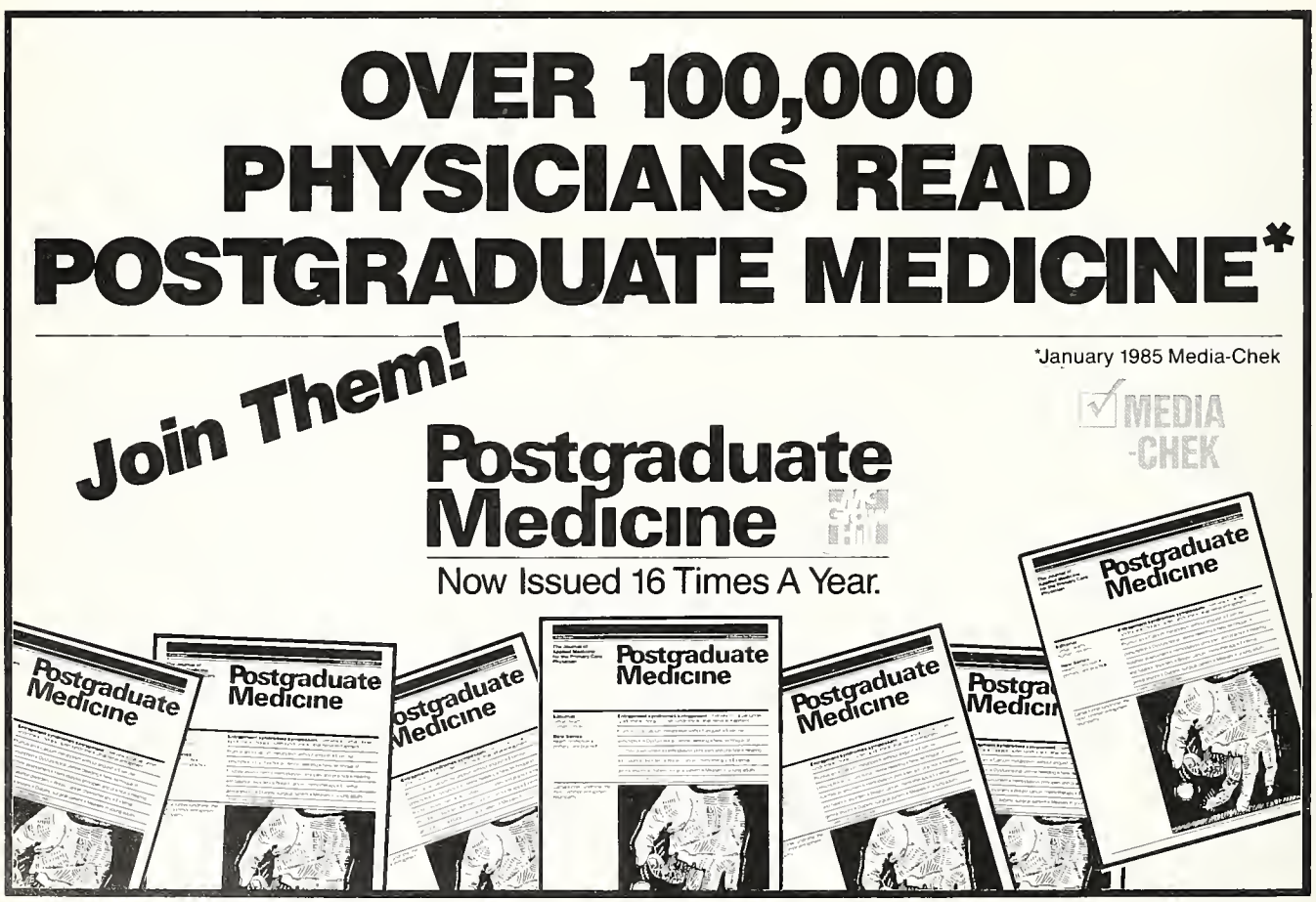
If you believe that immunizing your colleagues against civil liability will assist in keeping potentially unsafe drivers off the road, and that doing so will make a significant contribution toward reduction of the motor vehicle accident rate, then now is the time to make those beliefs known to a legislator. NCMS employs a staff in Raleigh willing and able to help you by providing names of legislators and advice about what to say or how to say it. Two very knowledgable individuals, Ann Sawyer, Governmental Affairs Director and Stan Williams, her Executive Assistant, can be reached at 1-800-722-1350.

These are risky times medically-legally speaking and many might doubt the capability of any law to provide protection against liability. Moreover, how one exercises medical discretion in reporting could potentially be cause for vulnerability to a lawsuit, especially if someone chooses to interpret a qualified privilege to report as a

From the Department of Medicine, Duke University Medical Center, Durham 27710.

requirement to do so. Although current malpractice trends and a climate of culpability threaten to poison our atmosphere, they shouldn't prevent a meaningful dialogue between physicians and legislators. After all, for centuries we have been burdened by sometimes knowing more than we'd like to about our patients' bodies and minds. If some of that knowledge could potentially be used to promote better health for society as a whole, it should be.

Since most people listen and learn best at a time when they must consider a specific problem, I have mentioned to several State Representatives and Senators my interest in specific issues and offered them a paging beeper number so that they can reach me whenever *they* are ready to discuss a medical matter.



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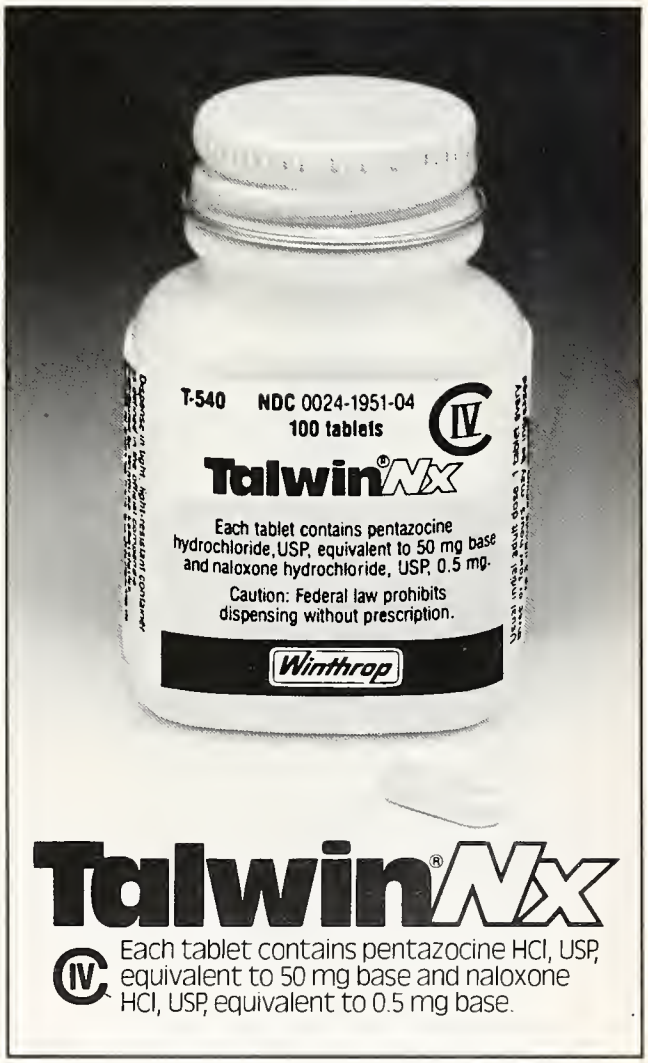
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The original formulation had been subject to a form of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ;* an antihistamine, would be ground up together, put into solution, and injected intravenously. The combination produced a heroin-like high. Because naloxone is a narcotic antagonist when injected intravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine in a combination of TALWIN Nx and PBZ. When taken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for the relief of moderate to severe pain, now providing added security against misuse.

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The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

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Please see following page for Brief Summary.

Talwin® Nx (IV)

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence.* Can cause physical and psychological dependence. (See **Drug Abuse and Dependence**.) *Head Injury and Increased Intracranial Pressure.* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Can obscure the clinical course of patients with head injuries; in such patients, use with extreme caution and only if deemed essential. *Usage with Alcohol.* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics.* Pentazocine is a mild narcotic antagonist. Withdrawal symptoms have occurred in patients previously given narcotics, including methadone. *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Precautions: *CNS Effect.* Use cautiously in patients prone to seizures; seizures have occurred though no cause and effect relationship has been established. Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours. Such patients should be very closely observed and vital signs checked; if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function.* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient. *Biliary Surgery.* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures; the clinical significance of these findings is not yet known. *Information for Patients.* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction.* Use with caution in patients with myocardial infarction who have nausea or vomiting. *Drug Interactions Usage with Alcohol.* See **Warnings**. *Carcinogenesis, Mutagenesis, Impairment of Fertility.* No long-term studies in animals to test for carcinogenesis have been performed. *Pregnancy Category C.* Should be given to pregnant women only if clearly needed. *Labor and Delivery.* Use with caution in women delivering premature infants. Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown. *Nursing Mothers.* Caution should be exercised when administered to a nursing woman. *Pediatric Use.* Safety and effectiveness in children below the age of 12 years have not been established.

Adverse Reactions: *Cardiovascular.* Hypotension, tachycardia, syncope. *Respiratory:* Rarely, respiratory depression. *CNS Acute CNS Manifestations.* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted. *Other CNS Effects:* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor. *Gastrointestinal.* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress. *Allergic:* Edema of the face, dermatitis, including pruritus; flushed skin, including plethora. *Ophthalmic:* Visual blurring and focusing difficulty. *Hematologic:* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other.* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance.* TALWIN Nx is a Schedule IV controlled substance.

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported. In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient. Tolerance to the analgesic effect is rarely reported; there is no long-term experience with oral use of TALWIN Nx.

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine; however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics. TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Overdosage: *Treatment.* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing.

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Drugs Worked But How? Frederick Bernheim Unravels The Mystery

Frederick Bernheim, Ph.D.

WHEN I joined the Duke faculty in 1930, the nature of enzymes and their actions were not understood. In many ways they were similar to inorganic catalysts which were known to speed up and facilitate many chemical reactions. The fact that a large number of different enzymes had to be present to carry out the many chemical reactions necessary for life within a narrow range of temperatures was beginning to be appreciated. No one had a clear idea of the materials and their organization which could lead to such diversity in structure and function. The notion that enzymes might be proteins was unthinkable. It was known that enzyme activity did not require live intact cells. They had the property described as *élan vitale*.

In the early 1930s Sumner[1] crystallized a protein obtained from bean meal, carefully purified it, and showed that it acted as an enzyme to break down urea into ammonium carbonate. He called the protein urease. His troubles then began. No journal would publish his paper because it was unthinkable that a pure protein could be a catalytic enzyme. Eventually, his work was published and confirmed. Sumner started an area of intensive work on enzymes, their purification, structure and mechanism of action. Enzymes in body fluids were more easily concentrated and purified than those present in cells. When one homogenized cells, he obtained a soup containing many enzymes besides the one the investigator wished to study.

At this time we knew that drugs caused changes in body functions but we did not know how those changes were produced. Could it be that drugs attached themselves to enzymes or to the substrate of enzymes and altered thereby certain chemical effects? We knew that various drugs added to homogenates of cells or purified enzymes inhibited activity of the enzyme. We found out that the inhibition showed specificity in that a drug rarely affects more than one enzyme. I asked the question: can the inhibition of the enzyme explain the pharmacological effects seen when the drug is given to the animal?

When I began the attempt to answer this question, an affirmative answer was found in only two instances. Eserine inhibits isolated cholinesterase and prolongs acetylcholine effects in the animal as shown by Loewi,[2] and cyanide inhibits cytochrome oxidase, the enzyme essential for cell respiration,[3] rapidly kills the animal. I decided that it would be pertinent to test the effect of a number of other drugs on enzymes and then search the literature to determine how far enzyme action correlates with pharmacological action. Enzymes and substrates were where the action was. In 1940 I wrote a monograph on the results of my and others' work. It was entitled *The Interaction of Drugs and Cell Catalysts* and was published in 1942. The following is the table of contents of the monograph.



Frederick Bernheim, Ph.D., was born into a middle-class family in Long Branch, New Jersey. His father was a native of New York, New York and his mother of Wilmington, North Carolina. He was educated in the Ethical Culture School, Andover, Harvard, Cambridge, England. He wanted to become an M.D. but his mother became one "after more or less raising me and two younger brothers. For complicated psychological reasons, this made it impossible for me to study medicine so I settled for a career in biomedical research." Professor Bernheim donated the original 70 acres for the Eno River Park in Durham.

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From the Department of Pharmacology, Duke University Medical Center, Durham 27710.

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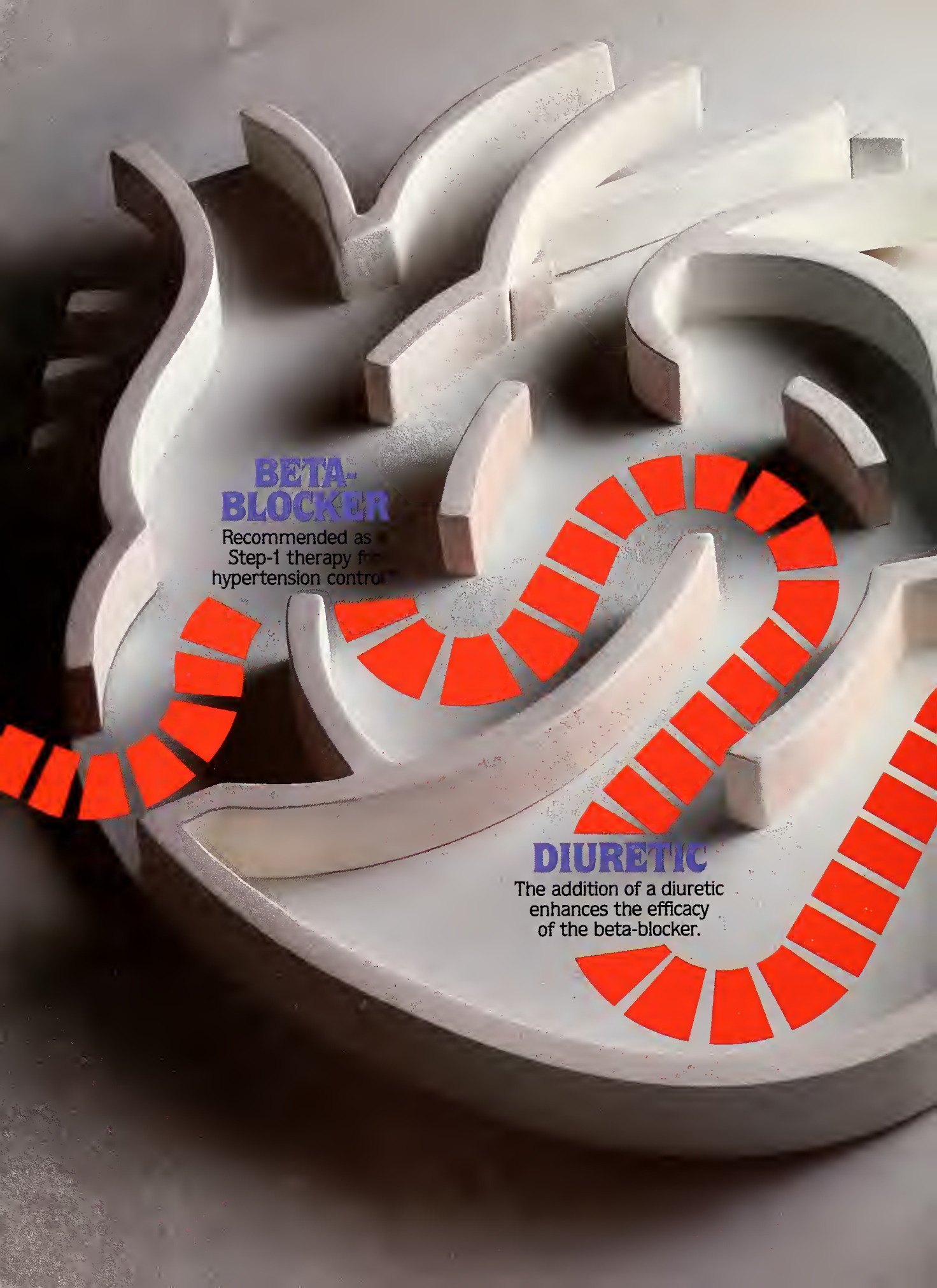
The appreciation of the great diversity of enzymes and the knowledge that the attachment of drugs to these structures would change their organization and activity has taken the mystery out of pharmacology and allowed understanding at the molecular level. I am pleased that my position in the Duke Medical School gave me a stable platform to explore basic pharmacology and to have a role in understanding how drugs have their effect.

References

1. Sumner JB. J Biol Chem 1926; 69:435.
2. Englehart E, Loewi O. Arch Exp Path Pharmacol 1930; 150:1.
3. Warburg O. Z Physiol Chem 1910; 70:413.

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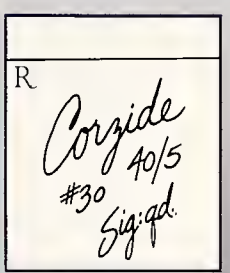
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*Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984.

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CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — Nadolol — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide*, and PRECAUTIONS, *General, Bendroflumethiazide).*

Drug Interactions — Nadolol — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents: **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery).* **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol, Diabetes and Hypoglycemia).* **Catecholemina-depleting drugs (e.g., resarpine)** — additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbituretes, or narcotics** — may potentiate orthostatic hypotension. **Antidiebetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticostaroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or paripheral adrenargic blocking drugs** — potentiated effect. **Preanasthatic and anasthatic agants** — effects may be potentiated; adjust dosage accordingly **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skalatel muscle relaxants, nondepolarizing (a.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interections — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide).*

Carcinogenesis, Mutaganesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazida** — Long-term studies in animals have not been performed

Pregnancy — Taretogenic Effects — Nadolol — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumathiazida** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus; these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cerdiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instences of first degree and third degree heart block have been reported. Intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin, impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Centrel Nervous System** — reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss; emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hemetologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash; arterial insufficiency.

Bendroflumethiazide — Gestrointestinal System — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hemetologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycerdie** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a β_2-stimulating agent and/or a theophylline derivative. **Stupor or Come** — Supportive therapy as warranted. **Gestrointestinel Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormelities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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Good Grief Makes Good Sense

J. Trig Brown, M.D.

It is as inevitable as death and taxes: we all have or will experience losses during our lives. Our normal and expected reaction to loss is called the grief reaction. This reaction is characterized by a series of feelings, both mental and physical, which, if allowed to be expressed, helps us adapt to the loss. Good grieving, that is, completely working through the stages of grief, is very important to long-term health. Although we usually only think of grief occurring after the death of a close acquaintance, the same feelings can and should follow any significant loss (financial, health, possessians, etc.). Moving through the stages of grief in a narmal fashion will be demanstrated in the following narrative.

The Normal Grief Reaction

Mrs. B., already nervous because her husband was unusually late this evening, had her greatest fears confirmed when she saw the State Trooper at her front door. "There has been an accident, Mrs. B., and I'm terribly sorry to have ta tell you that your husband has been killed," the Trooper began.

"Oh my God, no, it can't be true. . . . I just don't believe it," the distraught woman cried as the rest of the Trooper's message went unheard. Suddenly, calming herself, she motioned the Trooper in and asked him to repeat the story.

"There must be a mistake, how can you be sure it was my husband?" she replied. She listened and then rejected his story for a third time until a neighbor arrived. He, too, knew af the accident; in fact, he had positively identified the body. The tears on his face confirmed the Trooper's news and Mrs. B. sighed, shook her head, and then burst into uncontrollable sobbing.

The next few days passed in a blur for Mrs. B. She wonders how she had the strength to make the decisions regarding the funeral service, remembers hoping and praying that it had all been a mistake, and remembers the devastating feeling when, finally seeing her husband's body at the chapel, she could no longer deny his death.

This woman is experiencing that phase of the grief reaction known as the **Shock Phase.** This typically begins immediately after learning abaut the loss and lasts for a few days. The most striking feature of this period is to feel numb and for the loss to seem unreal. As demonstrated by the above narrative, Mrs. B. tended to not believe the news of her husband's death until she finally saw his body, thus undeniably confirming the reality of the loss.

This Shack Phase is protective. By holding on to partial hope that the loss is not real, we are able to function during the time immediately after the loss. If we did not have this protective numbing ability, the full sense of the loss would likely overwhelm most of us.

During this time sensations of thraat tightness, abdominal emptiness, poor appetite, and crying spells are common. As the numbness and sense of unreality gradually fade, the knowledge that the loss is real is solidified and we enter the second phase of the grief reaction, the **Preoccupation Phase.**

Mrs. B. looks back on the months following her husband's death as the mast difficult of her life. Thoughts of her husband were on her mind constantly. In the afternoons she would anticipate his return from work at the usual time and then, painfully remembering his death, tears would flow. Certain sights, sounds, and activities would bring a shower of painful memories of her husband. The memories felt when she glanced at their wedding picture were so sad and painful that she finally had to place it face down in a desk drawer.

She dearly loved her husband and yet some of the memories were not

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pleasant. They had had their normal share of conflicts and when she recalled those discussions she would feel an enormous amount of guilt. At times she even felt angry at him for leaving her and this served to make her feel even more guilty.

Often unable to sleep she would lay awake calling to mind times they had spent together. On a few occasions, she had vivid dreams of being with her husband and one time even had a strong sense that he was in the bed with her. In these dreams he appeared very comfortable and this left her with a peaceful feeling.

Mrs. B. found it difficult to resume participation in her usual activities and isolated herself socially. She did visit her doctor on two occasions because she had no appetite, had lost five pounds, and felt fatigued both day and night. After some blood tests the doctor reassured her that these symptoms were expected during this grieving period. Indeed, Mrs. B. found that these symptoms did lessen shortly after the doctor's visit.

Our narrative finds this recent widow in the midst of the second phase of the grief reaction, the **Preoccupation Phase.** This phase begins as the emotional "numbness" of the first phase lessens and the sense of the loss becomes more real. As in this example the grieving person is preoccupied with memories of the dead friend or relative. Every aspect of their lives together is relived through recalling past events.

In order to be able to form emotional attachments in the future, we must first give up the ties to the lost one. By moving through this second phase of grief the lost relationship is closely examined, the emotions stirred up by the loss are expressed, and gradually we are able to move forward again in life.

The feelings of sadness, anger, and even guilt are normal as past conflicts and problems are remembered. These feelings can be so strong and painful that the grieving individual might actually interrupt the grieving process at this time, resume normal activities too quickly, and thus be set up in the future for potential problems.

Some decrease in appetite and weight is normal during this phase. Sleep difficulty and vivid dreams of the deceased are not unusual. At times dreams can be so real that they take on a life-like character with visual images of the deceased. Weakness and fatigue are not uncommon during this second phase; however, these same symptoms can represent more serious medical problems and should be evaluated by a medical doctor if there is any question.

Gradually Mrs. B.'s life began to return to normal. As her sleeping approached normal, her weakness and fatigue waned. Dreams of her husband became rarer. Previous activities again became pleasing and she resumed many of her social activities.

This gradual improvement was interrupted by a return of the sleep difficulty, decreased appetite, and fatigue. Another visit to her doctor uncovered the fact that these symptoms were occurring at the first year anniversary of her husband's death. Again these symptoms went away on their own. She noticed similar but briefer difficulties at holiday times.

Although she still thought about her husband often, the memories gradually evoked less pain. She became able to think about past activities and places with pleasure and not with tears. Their wedding picture, stashed away because of the painful feelings seeing it produced, once again found its place on the desk.

The third and final phase of the grief reaction is the **Resolution Phase.** As the manifestations of the second phase gradually diminish we are less preoccupied with the thoughts of the deceased and less socially disabled. As Mrs. B.'s course demonstrates, the grieving individual may notice a return of the sadness, sleep difficulty, and other manifestations of the second phase of grief at certain significant times. These are known as "anniversary reactions" and examples include the anniversary of the death, the deceased's birthday and holidays. These setbacks are usually temporary and disappear on their own.

The length of the normal grief reaction varies; however, most note some progress toward resolution by at least six to eight months. By 12 months the grief reaction is usually completed and once again the person is able to think about the past with pleasure, activities that had been curtailed are again interesting, and new relationships can be formed.

Guidelines for Good Grieving

Time normally heals the wounds of losses. There are some people, however, who do not proceed through the phases of grief normally. These people may develop depression, social isolation, difficulties with other relationships, and other medical problems in the future because of this incomplete grieving. During the grieving period it is difficult for the person closest to the loss to recognize an abnormal grief response; thus these guidelines are being presented for those close to the person who has experienced the loss. With these points in mind we may better be able to help our friends, family members, and perhaps ourselves to cope with losses.

1. Prepare

Although some losses are sudden and unexpected, the majority of losses we experience can to some degree be anticipated. Preparing for future losses is called "anticipatory grief" and helps adjust to the loss once it occurs. During a lengthy terminal illness we should be talking with our

loved ones, expressing both the joys of having them and the anticipated sorrows of being apart. We should ensure that things we want to say to this person are said; it is much better to know that you have expressed yourself than to have to hope that they somehow knew what you wanted to say. Get financial affairs in order; knowledge of financial stability for dependents is very comforting to most terminally ill people. By all means do not shun the topic of the person's illness. If a terminally ill person senses that you cannot deal with the issue, he or she may have more difficulty in coping also.

2. Grieve

Not grieving is bad grieving. We have all seen the person who showed little or no emotional reaction to a loss. "She surprised us; she was so strong and didn't break down and fall apart," may be a harbinger of problems and not necessarily a statement of strength. It should be stressed again that the grief reaction is normal and necessary and absent grief may mean that the person is too overwhelmed by the painful emotions produced by thinking about the loss to allow any expression of sadness. These people, by denying the truth of the loss, are at risk to develop problems in the future. People who express no grief should be encouraged to discuss what the loss means to them, in this supportive way hearing that it is okay to grieve.

3. Talk

Talking is the best way to ensure that the grief reaction proceeds normally. People with recent losses should be encouraged to talk about the loss, their life before and after the loss, and to express the emotions that surge forth when discussing these issues. Sharing feelings and experiences and crying together is beneficial. Anger and guilty feelings may make it too painful for these issues to be discussed. In such cases talking to professional counselors is helpful.

4. Participate

In our society there are a number of rituals which assist our grieving. Full participation in these activities should be encouraged. Viewing the body, the memorial service, and the graveside ceremony help us grasp the reality of the loss and move the grief reaction forward. After a loss, family and friends gather, thus adding social support to those who are in need. Business matters and financial affairs often require attention and the recently bereaved should participate in these. Articles of clothing and possessions should be sorted through, saving some and giving others away. This act helps start the process of sorting through memories, a crucial step in getting over the loss. At every stage in the grieving process we should urge the active participation of those involved.

Prepare, grieve, talk, and participate are four actions that will help the grief reaction flow in a normal manner. The overall goal is to allow us to examine our emotional attachments and to express the feelings that the loss produces. Through this process, we will then be able to adjust to the changes created by the loss. We should prevent abnormal grief reactions because they can have detrimental effects upon health. If you have questions about your own reaction to loss or about a friend's or family member's reaction, ask your doctor. This health issue deserves attention.

When To See Your Doctor About Vertigo and Dizziness

Marvin P. Razear, M.D.

Vertigo means an abnormal feeling that you are standing still and other things are moving or vice versa (when your intellect tells you that neither you nor your surroundings are moving). This is the feeling you get after you spin around in circles a few times, or get off a merry-go-round. In strictest terms, it is an illusion or hallucination (of movement).

Dizziness is a more nonspecific term which includes vertigo, but also a lot of other things people call lightheadedness, wooziness, faintness, but which do not necessarily include the illusion of motion. Some authorities say vertigo is more often due to actual disturbance of the balance organs of the inner ear or their brain connections, while dizziness is more nonspecific and more often due to other factors which affect the whole brain diffusely, such as low blood sugar, low blood pressure, fainting, nervousness, etc.

In my experience, the distinction does not carry much weight: some people who have clear-cut disturbances of their inner ears report that they were just woozy but not experiencing the sensation of motion. Furthermore, the only time I ever fainted, due to a sudden drop in blood pressure, I clearly experienced the room as spinning around. I remember it vividly. The room was going right to left.

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The point is that the exact quality of the symptom may not be so terribly important. Well then, what is? I feel three things are important: (1) the progression of the dizziness, (2) what brings on the dizziness and (3) what it is associated with.

Using these features, I think we can construct a list of things which indicate that the dizziness requires medical attention, and these include:

1) constant or progressive dizziness, especially associated with hearing loss;

2) dizziness associated with other symptoms such as visual disturbance (especially double vision), numbness, or weakness in any body part;

3) dizziness associated with recurrent vomiting;

4) dizziness which lasts for more than a few seconds on standing up.

There are some types of dizziness that are much more benign and don't necessarily warrant medical attention:

1) intermittent dizziness with long periods of well-being between spells;

2) dizziness which comes on only in certain positions (especially lying down certain ways) and goes away in 10-20 seconds even though you maintain this position;

3) the dizziness associated with certain activities such as riding in the back seat of a car or looking down from high places.

If you feel that your dizziness falls into the "bad" category above, and that it warrants medical attention, the next question that comes up is "how soon should I seek medical attention?" We can be guided by the degree of sickness experienced here: If this has been slowly progressing over several months and has not yet caused any great disability, you could make an appointment with a physician and be seen in the next few weeks. On the other hand, if you are suddenly seized in the morning by intense dizziness associated with severe nausea, vomiting, double vision, and a headache, you should go to the nearest emergency facility as soon as possible.

One more comment. Dizziness can be a very difficult symptom for patients to deal with and communicate about and therefore many doctors are uncomfortable in trying to help dizzy patients. If time permits and your dizziness does not seem to be an urgent or emergent problem, you might do well to ask around and find out if there is a doctor in your community or nearby who has shown an interest in dizziness or who has been helpful to a friend or neighbor in the past. Frequently, neurologists or otolaryngologists are more interested in dizziness than are other doctors, although this is certainly not an absolute rule.

Rubella Prevention

Live Rubella Virus Vaccine

The live virus vaccine* currently distributed in the United States is prepared in human diploid cell culture. In January 1979, this vaccine (RA 27/3) replaced the HPV-77:DE-5 vaccine grown in duck embryo cell culture. Although both subcutaneous and intranasal administration of the vaccine have been studied, it is licensed only for subcutaneous administration. The vaccine is produced in monovalent form (rubella only) and in combinations: measles-rubella (MR), rubella-mumps, and measles-mumps-rubella (MMR) vaccines.

In clinical trials, 95% or more of susceptible persons who received a single dose of rubella vaccine when they were 12 months of age or older developed antibody. Clinical efficacy and challenge studies have shown that more than 90% of vaccinees can be expected to have protection against both clinical rubella and asymptomatic viremia for a period of at least 15 years. Based on available followup studies, vaccine-induced protection is expected to be lifelong. Therefore, a history of vaccination is presumptive evidence of immunity.

Although vaccine-induced titers are generally lower than those stimulated by rubella infection, vaccine-induced immunity usually protects against both clinical illness and viremia after natural exposure. There have been, however, a small number of reports indicating that viremic reinfection following exposure may occur in vaccinated individuals with low levels of detectable antibody. The frequency and consequences of this phenomenon are currently unknown, but its occurrence is believed rare. Such reports are to be expected, since there are also rare reports of clinical reinfection and fetal infection following natural immunity.

Some vaccinees intermittently shed small amounts of virus from the pharynx 7-28 days after vaccination. However, studies of more than 1,200 susceptible household contacts and experience gained over 15 years of vaccine use have yielded good evidence that vaccine virus is not transmitted. These data indicate that vaccinating susceptible children, whose mothers or other household contacts are pregnant, does not present a risk. Rather, vaccination of such children provides protection for these pregnant women.

Vaccine Shipment and Storage

Administering improperly stored vaccine may result in lack of protection against rubella. During storage, before reconstitution, rubella vaccine must be kept at 2°C-8°C (35.6 F-46.4 F) or colder. It must also be protected from light, which may inactivate the virus. Reconstituted vaccine should be discarded if not used within 8 hours. Vaccine must be shipped at 10°C (50 F) or colder and may be shipped on dry ice.

Vaccine Use

General Recommendations

Persons 12 months of age or older should be vaccinated, unless they are immune. Persons can be considered immune to rubella only if they have documentation of

1. laboratory evidence of rubella immunity or
2. adequate immunization with rubella vaccine on or after the first birthday. The clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status.

All other children, adolescents, and adults — particularly women — are considered susceptible and should be vaccinated if there are no contraindications (see below). This includes persons who may be immune to rubella but who lack adequate documentation of immunity. Vaccinating children protects them against rubella and prevents their spreading the virus. Vaccinating susceptible postpubertal females confers individual protection against rubella-induced fetal injury. Vaccinating adolescent or adult females and males in high-risk population groups, such as those in colleges, places of employment, or military bases, protects them against rubella and reduces the chance of epidemics. This is exemplified by the experience with vaccinating all military recruits, which has virtually eliminated rubella from military bases. Similar results could be achieved by ensuring proof of immunity of all employees, all college students and staff, and all hospital personnel, including physicians, nurses, health-profession students, technicians, dietary workers, etc.

As discussed above, it is generally believed that any detectable antibody titer specific for rubella (whether resulting from vaccination or from naturally acquired rubella), even if very low, should be considered evidence of protection against subsequent viremic infection — including the reported "reinfection" of persons with low levels of antibody demonstrated by boosts in antibody titer. This suggests that immune females reinfected during pregnancy would be unlikely to infect their fetuses. Moreover, because there is very little pharyngeal excretion, there appears to be no risk to susceptible contacts in such reinfection

* Official name: Rubella Virus Vaccine, Live. From Morbidity and Mortality Weekly Report, June 8, 1984.

settings. In view of the data on reinfection accumulated during the past decade the Immunization Practices Advisory Committee (ACIP) sees no reason to revaccinate persons with low levels of rubella antibody. Rather, more attention should be directed toward vaccinating the truly susceptible population.

Dosage

A single dose of 0.5 cc of reconstituted vaccine (as a monovalent or preferably a combination product such as MR or MMR) should be administered subcutaneously.

Age at Vaccination

Live rubella virus is recommended for all children 12 months of age or older. It should not be given to younger infants, because persisting maternal antibodies may interfere with seroconversion. When the rubella vaccine is part of a combination that includes the measles antigen, the combination vaccine should be given to children at 15 months of age or older to maximize measles seroconversion. Older children who have not received rubella vaccine should be vaccinated promptly. Because a history of rubella illness is not a reliable indicator of immunity, all children should be vaccinated unless there are contraindications (see below).

Vaccination of Women of Childbearing Age

The ACIP has weighed several factors in developing recommendations for vaccinating women of childbearing age against rubella. Although there may be theoretical risks in giving rubella vaccine during pregnancy, available data on previously and currently available rubella vaccines indicate that the risk, if any, of teratogenicity from live rubella vaccines is quite small. As of December 31, 1983, CDC has followed to term 214 known rubella-susceptible pregnant females who had been vaccinated with live rubella vaccine within 3 months before or 3 months after conception. Ninety-four received HPV-77 or Cendehill vaccines, one received vaccine of unknown strain, and 119 received RA 27/3 vaccine. None of the 216 babies (two of the mothers receiving RA 27/3 vaccine delivered twins) has malformations compatible with congenital rubella infection. This finding includes the four infants born to these susceptible women who had serologic evidence of subclinical infection. (Three of the infants were exposed to HPV-77 or Cendehill vaccine; one was exposed to RA 27/3 vaccine.)

Based on the experience to date, the maximum estimated theoretical risk of serious malformation attributable to RA 27/3 rubella vaccine, derived from the binomial distribution, is 3%. (If the 95 susceptible infants exposed to other rubella vaccines are included, the maximum theoretical risk is 1.7%). However, the observed risk with both the HPV-77 or Cendehill and RA 27/3 strains of vaccine is zero. In either case, this risk is far less than the 20% or greater risk of congenital rubella syndrome associated with maternal infection during the first trimester of pregnancy.

Although experience with the RA 27/3 vaccine is more limited than that with the other rubella vaccines, rubella vaccine virus has been isolated from abortion material from one (3%) of 32 susceptible females who had been given RA 27/3 vaccine while pregnant, whereas virus was isolated from abortion material from 17 (20%) of 85 susceptible females who had been given HPV-77 or Cendehill vaccines while pregnant. This provides additional evidence that the RA 27/3 vaccine does not pose any greater risk of teratogenicity than did the HPV-77 or Cendehill vaccines.

Therefore, the ACIP believes that the risk of vaccine-associated defects is so small as to be negligible and should not ordinarily be a reason to consider interruption of pregnancy. However, a final decision about interruption of pregnancy must rest with the individual patient and her physician.

The continuing occurrence of rubella among women of childbearing age and the lack of evidence for teratogenicity from the vaccine indicate strongly that increased emphasis should continue to be placed on vaccinating susceptible adolescent and adult females of childbearing age. However, because of the theoretical risk to the fetus, females of childbearing age should receive vaccine only if they say they are not pregnant and are counseled not to become pregnant for 3 months after vaccination. In view of the importance of protecting this age group against rubella, reasonable practices in a rubella immunization program include: (1) asking females if they are pregnant, (2) excluding those who say they are, and (3) explaining the theoretical risks to the others.

Use of Vaccine Following Exposure

There is no conclusive evidence that giving live rubella virus vaccine after exposure will prevent illness. Additionally, there is no evidence that vaccinating an individual incubating rubella is harmful. Consequently, since a single exposure may not cause infection and postexposure vaccination will protect an individual exposed in the future, vaccination is recommended, unless otherwise contraindicated.

Use of Human Immune Globulin Following Exposure

Immunoglobulin (IG) given after exposure to rubella will not prevent infection or viremia, but it may modify or suppress symptoms and create an unwarranted sense of security. The routine use of IG for postexposure prophylaxis of rubella in early pregnancy is not recommended. Infants with congenital rubella have been born to women given IG shortly after exposure. IG might be useful only when a pregnant woman who has been exposed to rubella would not consider termination of pregnancy under any circumstances.

Recent Administration of IG

Vaccine should be administered about 2 weeks before or deferred for about 3 months after receipt of IG, because passively acquired antibodies might interfere with the response to the vaccine. On the other hand, previous administration of anti-RJo (D) immune globulin (human) or blood products does not generally interfere with an immune response and is not a contraindication to postpartum vaccination. However, in this situation, 6- to 8-week postvaccination serologic testing should be done on those who have received the globulin or blood products to assure that seroconversion has occurred. Obtaining laboratory evidence of seroconversion in other vaccinees is not necessary.

Side Effects and Adverse Reactions

Children sometimes have vaccine side effects, such as low-grade fever, rash and lymphadenopathy. Up to 40% of vaccinees in large-scale field trials have had joint pain, usually of the small peripheral joints, but frank arthritis has generally been reported far fewer than 2%. Arthralgia and transient arthritis occur more frequently and tend to be more severe in susceptible women than in children. While up to 3% of susceptible children have been reported to have arthralgia, arthritis has rarely been reported in these vaccinees. By contrast, up to 10%-15% of susceptible female vaccinees have been reported to have arthritis-like signs and symptoms. Transient peripheral neuritic complaints, such as paresthesias and pain in the arms and legs, have also very rarely occurred.

When joint symptoms or nonjoint-associated pain and paresthesias do occur, they generally begin 3-25 days (mean 8-14 days) after immunization, persist for 1-11 days (mean 2-4 days) and rarely recur. Adults with joint problems usually have not had to disrupt work activities. The occasional reports of persistent or recurrent joint signs and symptoms probably represent a rare phenamenon. No joint destruction has been reported. While the presence of immune complexes following vaccination has been reported to be associated with arthralgia and arthritis, the available data are still inconclusive. Comparable studies on naturally infected persons have not been conducted. Likewise, there is no clear association between joint symptoms and persistence of rubella virus in lymphocytes.

The vast majority of published data indicate that only susceptible vaccinees have side effects of vaccination. There is no conclusive evidence of an increased risk of these reactions for persons who are already immune when vaccinated.

Although vaccine is safe and effective for all persons 12 months of age or older, its safety for the developing fetus is not fully known. Therefore, though the risk, if any, appears to be minimal, rubella vaccine should not be given to women known to be pregnant because of the theoretical risk of fetal abnormality caused by vaccine virus (see above).

Precautions and Contraindications

Pregnancy

Pregnant women should not be given rubella vaccine. If a pregnant woman is vaccinated or if she becomes pregnant within 3 months of vaccination, she should be counseled on the theoretical risks to the fetus. As noted above, rubella vaccination during pregnancy should not ordinarily be a reason to consider interruption of pregnancy. Instances of vaccination during pregnancy should be reported through state health departments to the Division of Immunization Center for Prevention Services, CDC.

Because of the increasing number of cases reported to CDC, the experience with known susceptibles is becoming well defined. Therefore, CDC now encourages reporting only cases involving women known to be susceptible at the time of vaccination.

Febrile Illness

Vaccination of persons with severe febrile illness should be postponed until recovery. However, susceptible children with mild illnesses, such as upper respiratory infection, should be vaccinated. Considering the importance of protecting against rubella, medical personnel should use every opportunity to vaccinate susceptible individuals.

Allergies

Hypersensitivity reactions very rarely follow the administration of live rubella vaccine. Most of these reactions are considered minor and consist of wheal and flare or urticaria at the injection site.

Live rubella vaccine is produced in human diploid cell culture. Consequently, a history of anaphylactic reactions to egg ingestion needs to be taken into consideration only if measles or mumps antigens are to be included with rubella vaccine.

Since rubella vaccine contains trace amounts of neomycin (25 μg), persons who have experienced anaphylactic reactions to topically or systematically administered neomycin should not receive rubella vaccine. Most often, neomycin allergy is manifested as a contact dermatitis, which is a delayed-type (cell-mediated) immune response, rather than anaphylaxis. In such individuals, the adverse reaction, if any, to 25 μg of neomycin in the vaccine would be an erythematous, pruritic nodule or papule at 48-96 hours. A history of contact dermatitis to neomycin is not a contraindication to receiving rubella vaccine. Live rubella vaccine does not contain penicillin.

Altered Immunity

Replication of live rubella vaccine virus may be potentiated in patients with immune deficiency diseases and by the suppressed immune responses that occur with leukemia,

lymphoma, generalized malignancy, ond theropy with corticosteroids, alkylating drugs, antimetabolites, and radiation. Potients with such conditions should not be given live rubella virus voccine. Since vaccinated persons do not transmit vaccine virus, the risk to these potients of being exposed to rubella may be reduced by voccinoting their close susceptible contocts. Management of such patients, should they be exposed to rubella, can be facilitated by prior knowledge of their immune status.

Potients with leukemia in remission whose chemotherapy has been terminated for at least 3 months may receive live virus vaccines for infections to which they ore still susceptible (i.e., have neither had the disease nor the voccine before developing leukemia). The exoct interval after discontinuing immunosuppression that coincides with the obility to respond to individual vaccines is not known. Experts vary in their judgments from 3 months to 1 year.

Short-term (less thon 2 weeks) corticosteroid therapy, topical steroid therapy (e.g., nosol, skin), ond intro-articular, bursal, or tendon injection with corticosteroids should not be immunosuppressive ond do not necessorily controindicate live virus vaccine administrotion. However, live vaccines should be avoided if systemic immunosuppressive levels ore reached by topical application.

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See following page for brief summary of prescribing information.

SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

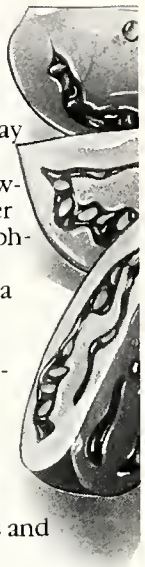
SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

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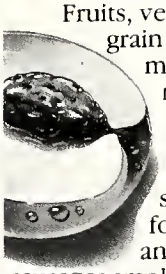
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There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash, and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.



Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

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Keats, Socrates and Fool's Parsley—Water Hemlock Poisoning

Ronald B. Mack, M.D.

ALL right Mack, this time you have gone too far. Socrates and hemlock, OK, but not Keats. You are really pushing it boy!!

To my detractors let me just say — a pox on your house!! John Keats, after all, was a "brother" and he did write a poem referring to the hemlock. That's right — he was a doctor. No, he did not graduate from Bowman Gray or Duke or Loyola or even the University of Texas, but he did devote five years of his life to studying medicine — 4 years as an apprentice to the apothecary-surgeon Thomas Hammond and 1 year at Guy's and St. Thomas' hospitals in London. While a student, he began to write poetry and at the age of 21 years, in 1816, he chose poetry as his profession instead of surgery (the DRGs must have really been tough back then). Don't you envy him, just a little?

John Keats is considered one of the greatest poets in the English language. His most beloved poem is thought to be "Ode To A Nightingale" which begins, as you remember so well, "My heart aches, and a drowsy numbness pains my sense, as though of hemlock I had drunk. . . ." Apparently Keats kept his medical texts and wove medical and scientific ideas into his poetry. He continued, even as a poet, to diagnose and treat his friends' maladies (he was fully licensed). Alas, he could not save himself, however, and died in 1821 at the age of 26 years of tuberculosis. He is buried in Rome and hard by the Spanish Steps in that beautiful city is a marker on the door of the dwelling in which he spent the last part of his short, productive life. He was, after all, the classic example of an oxymoronic poet (enough of that — it is shameful to speak of the dead in such a derogatory manner). No, no, no — *oxymoron* is the Greek word for a phrase that unites two contradictory ideas in a single meaningful term, e.g., delightful IRS agents.

The poisons we are discussing today are part of the same family that brought you celery, parsnip, parsley and carrots. The bad members of the family are the hemlock brothers (poison and water) and Fool's parsley. All three of these beauties are potentially fatal if ingested but the *water hemlock* (Cicuta maculata) is considered by the experts to be the most dangerous and, in fact, just may be the most poisonous plant in North America. In order for me not to get confused I am going to limit most of my remarks to this plant. But first a disclaimer — the plant known to many, many people as hemlock is in fact the hemlock tree, which is *harmless*.

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

The water hemlock, AKA beaver poison, cowbane, poison parsnip, etc. is approximately three to seven feet tall with quite distinctive roots and stems. The lower stem is usually thick and joins to a multiple root that resembles a bunch of carrots. When the stem is cut a yellow oily sap extrudes (Ugh!!) which has the odor of raw parsnips. At least the flowers are pretty; small, white, heavily scented flowers which grow in umbrella-like clusters known as umbrels. This plant usually grows only in wet areas such as marshes, swamps and creek banks.

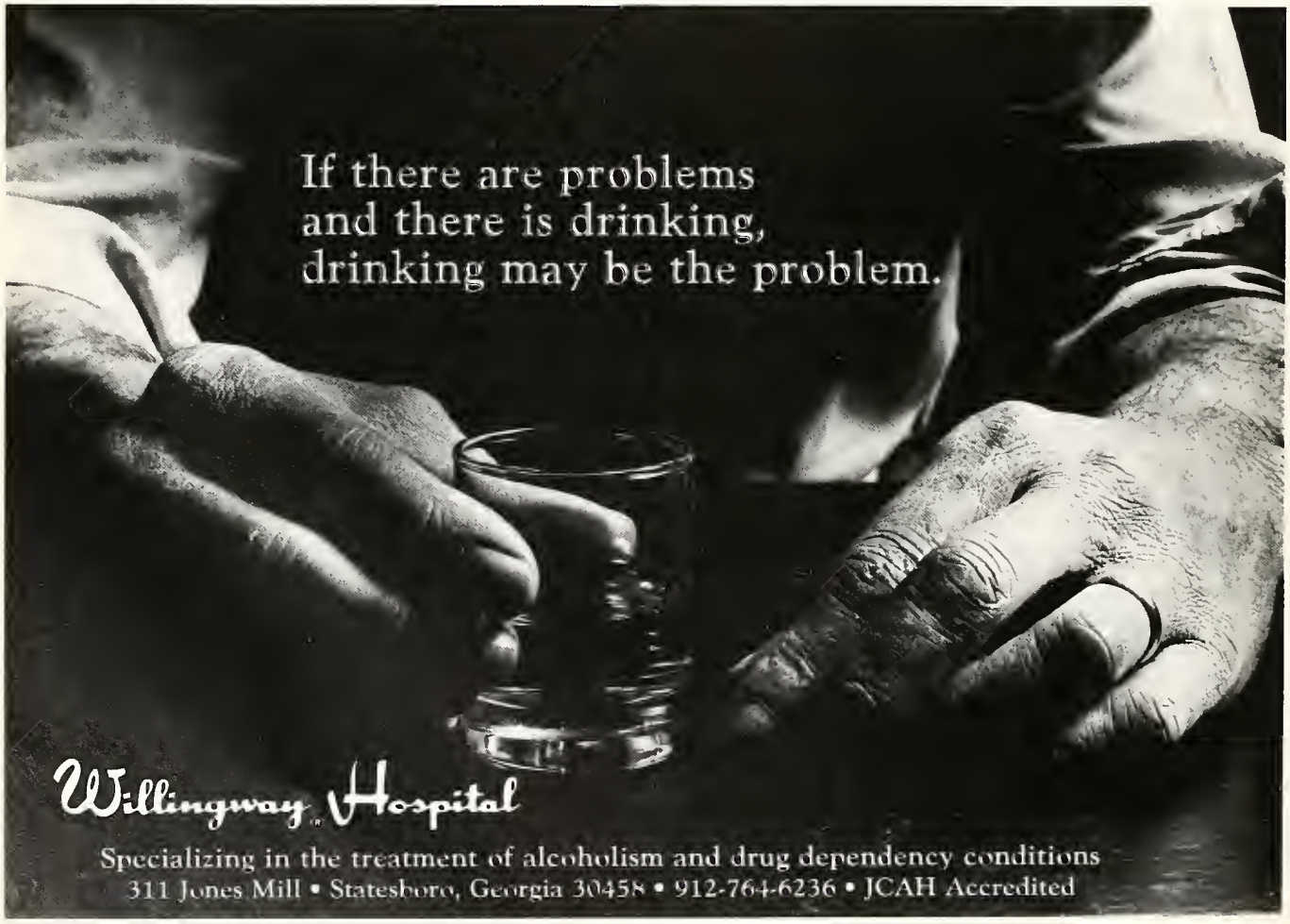
The entire plant is poisonous and not suitable for human consumption but the roots are the most poisonous sections. These roots resemble parsnips or wild carrots and are mistakenly picked by the unwary to eat. The toxic ingredient is an unsaturated aliphatic alcohol called *cicutoxin*. One bite-sized piece of the root can kill an otherwise healthy adult; a piece of root the size of a walnut can kill a cow and a single root has been known to do in a horse. The hollow stems can be used to construct whistles, which have caused death in children — we are talking dangerous plant here.

If you accidently chew this stuff up and swallow it, within 15-60 minutes you get very nauseated, with increased salivation and emesis. Many patients describe a burning sensation in the mouth and dysphagia. Tremors can occur in this initial phase of the poisoning. Then severe abdominal cramps and violent emesis ensue as well as diarrhea and this is the good news because the emesis can remove any material from the plant remaining in the upper gastrointestinal tract. The bad news is that seizures occur in this phase and these are probably best described as severe with violent clenching of the teeth, intense muscle spasms, convulsions that are grand-mal like and opisthotonus. At this point the victim is usually unconscious, the pulse is slow and weak and respiration is depressed. Delirium is very common in those still conscious. Death from cardiorespiratory failure can occur as early as 15 minutes post ingestion or as late as 8 hours after eating the plant. The pupils are typically dilated but my pupils got dilated by merely reading about this horrible flora. Needless to say, you would expect the CPK to be elevated after all this jumping around and it is. You need to observe the patient for myoglobinuria. Some impairment of mentation can be seen in survivors. It is of interest that the principal plant in the United States responsible for producing convulsions as the primary toxic event is the water hemlock.

The treatment of the poisoning that results from this extremely dangerous plant is symptomatic — no magic antidote here. If vomiting has not already occurred by the

time you are consulted (unlikely in view of its very irritative effect on the GI tract and rapid onset of action) and if the patient is alert, gastric emptying via ipecac induced emesis can be performed. The big challenge therapeutically is the cessation of the seizures and rapidly acting intravenous anticonvulsants seem to be the way to go. Many authors prefer parenteral diazepam (Valium) for this purpose; others prefer intravenous barbiturates such as thiopentone sodium. The constant seizure activity can cause an outstanding metabolic acidosis for which sodium bicarbonate may be required. Some authorities maintain that the spasms and convulsions that occur in this poisoning are the most violent they have ever seen with any disease.

Well, how about Socrates? That's what I say, how about Socrates? If the truth were known he did die from drinking hemlock but it was *poison hemlock*, not water hemlock. This plant is a common weed that grows up to eight feet tall and is found in waste areas of our country. It was apparently popular in ancient Greece as a method for inducing death by suicide, homicide, execution, etc. Reported instances of severe poisonings in this country from poison hemlock are quite uncommon; the Greeks on the other hand were apparently quite happy with its lethal qualities. Socrates was about 70 years old in 399 B.C. when he was executed for corrupting the youth of Athens. What he actually taught was hardly corrupting or seditious — he merely taught that students should doubt undocumented statements and that ideas should be clarified by means of rational answers to rational questions. One of his better dictims was "an unexamined life is not worth living." Heck, I say that all the time; well I didn't say it yesterday, but. . . .



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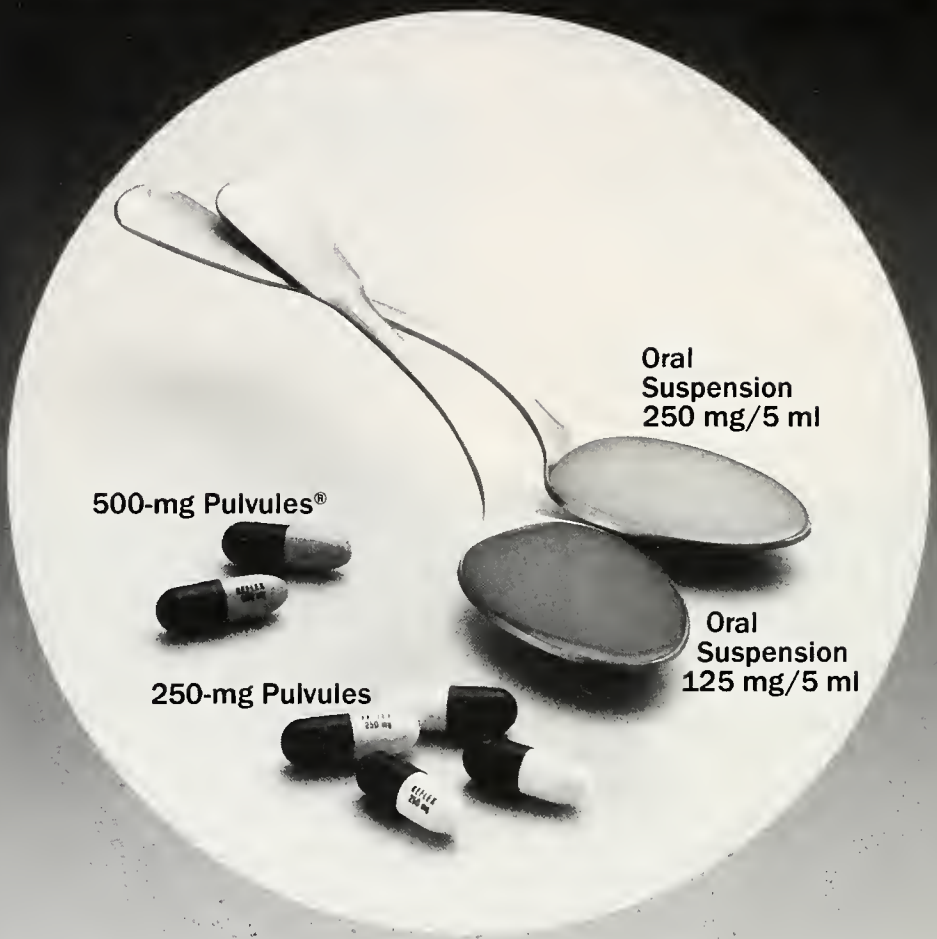
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Why an Army Medical Reserve?

W. Grimes Byerly, M.D.

IN the last several years any monthly issue of the *North Carolina Medical Journal* will contain three, four, or five full page advertisements from the Army, Navy and Air Force with the purpose of interesting physicians to join either the Active Component or Reserve Component Medical Corps of the various services.

At the annual meeting of the North Carolina Medical Society there are always two or three booths dedicated to military medical recruiting.

For approximately five years the United States Army has dedicated an individual officer recruiter to the State of North Carolina. His sole job is to recruit physicians for active duty Army Medical Service and assist the Medical Reserve forces in the State in their recruiting efforts.

The need for physicians in the military has existed from the beginning of our nation, and various techniques have been employed over the years to meet this need. With the advent of the Second World War, the general ground swell of patriotism and the intellectual knowledge that physicians were needed, the country achieved its necessary military medical personnel without a great deal of difficulty.

Major General Leonard Wood in 1916 wrote, "Behind the Regular Army must always stand the great Reserve Army consisting of the able-bodied men of the nation, so trained as to be promptly available for military service as needed but following their normal occupations in times of peace."

As a matter of history, the entire Reserve structure of the American Military was begun with the passage of Senate Bill 1424 on the 23rd of April, 1908, which authorized the Secretary of War to establish an Army Reserve Corps of Medical Officers who could be ordered to active duty in the time of emergency. Within a year over 300 men had been commissioned into the Medical Reserve Corps including such distinguished persons as Dr. Roswell Park, the surgeon who had attended President McKinley, and Dr. Wythe and Dr. Bryan, former Presidents of the American Medical Association.[1]

There has never been a tradition of a large peacetime standing Army or for that matter even a large Reserve force. During a time of crisis or war the mobilization of the untrained civilian community was the method the United States used to achieve a large military force. Until the close of the Second World War, the United States had always been allowed the luxury of time to produce the weapons and men necessary to fight its wars. Following the close of World War II, with the fact that the burden of Western societal defense militarily would fall increasingly on the United States and the luxury of time and distance would not be available, the American military had to restructure itself along with the consensus and direction of the American public as to how large a standing Army and standing Reserve force are both needed and allowable.

As is well known following the Second World War, the military physician supply was kept in a correct posture at least numerically, with the use of the civilian draft. Although the medical profession occasionally cried out its discomfiture because of the double jeopardy placed upon physicians in having to potentially serve their military obligations as non-physicians and then repeat it later on as a doctor, the situation continued to exist until the early 1970s.

The present problems and challenges of the Army Medical Reserve more or less began when President Nixon campaigned on a theme of ending the draft in 1968. During the years of winding down the Vietnam War, President Nixon directed (former) Secretary of Defense, Thomas S. Gates, Jr., to develop a comprehensive plan to eliminate conscription and establish an all volunteer force. The Gates Committee reported out in February 1970 that the all volunteer force should be just that and not a mixed force of conscripts and volunteers. The emphasis was upon the active force with little attention paid to the reserve components because a lack of data made it difficult to assess the impact of the volunteer army upon the Reserves. Concomitant with this the Army Chief of Staff, General William C. Westmoreland, issued a memorandum establishing that the reserve components must be considered the initial and primary source of additional units and individuals in any future rapid mobilization and directed Army planning predicated on this concept.[1] In the fall of 1970 the Army scaled down on withdrawal from Vietnam. To accomplish the reduction in size, units with service and support capabilities were removed from active duty and placed in the reserve structure. Money required for modernization was saved. With the abolition of the draft and the attempt to attain a volunteer army, a disastrous decade followed for the Army Medical Corps and in particular the Reserve Medical Corps.

As the civil unrest of the late 1960s stimulated a political decision to go to the all volunteer force, the fiscal realities of the early 1970s prompted the Army's total force policy. The reservist receives approximately 15% of the pay of an active duty soldier and, likewise, reserve units have lower operational and maintenance costs. It is estimated that the cost of maintaining approximately 500,000 reservists in the Ready Reserve is approximately one-tenth of that of main-

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Dr. Byerly serves his country as Col. Wesley G. Byerly MC USAR, Commanding Officer, 3274 USA Hospital, Durham, NC.

taining a similar number of men and women on active duty.

In an excellent and just recently published book on the history of the Army Reserve, the authors have presented a convincing case for the Reservist being *Twice the Citizen.*[1] Our country can no longer fight wars with minutemen militia picking up their muskets and marching off to a battle a few hundred miles away to be sustained by the local economy. The complexities of modern warfare require that those who fight in whatever manner, be it the use of the rifle, the typewriter, the x-ray machine, the computer, or whatever, be trained at the moment they begin their service and know exactly how to fit into the pattern of useful service from the start. We know that the tools of war are different and we know that wars will be "come as you are." For that reason an Army Medical Reserve instantly available is a vital necessity for the care of the injured of our future battles and wars.

Nearly two-thirds of the Army field hospitals and more than 40% of non-hospital medical units are manned by Army Reservists. Of all the military skills that are needed most after mobilization, the most difficult to recruit and retain are those of the varied medical specialties.

Phrased in another way, the fact that 66% of the active Army's medical assets and support are in the Reserve structure points up the absolute necessity for maintaining an adequate Reserve! The dependence by the Army on the Reserve to perform this mission makes obtaining professional medical people an immensely important task. This dependence of the Army upon the Reserve structure is vital in the early 1980s and, indeed, Lt. General William R. Richardson in addressing the Association of the United States Army in October 1982 categorically stated that the Army's ability to fight a war without the Reserves was zero.

Encouragingly, there has been a significant growth in Reserve Army health care professionals. Nursing strength is up to more than 79% of authorized levels from barely half strength just five years ago. Our overall physician strength now stands at 62%, up from less than 30% just four years ago.

All major Army Reserve Medical Units are commanded by physicians who are commissioned as Medical Corps Officers in the Army Reserve. The units are located in and near most major cities in the United States and through organizational exchange and management a physician may be placed in one unit geographically far away and work and train and participate in another that is physically closer for him.

Specific questions such as rank at time of commissioning, the amount of pay, creditable years of service for retirement, etc., are outside the scope of this particular discussion. However, given all the needed information, the special AMEDD physician recruiters scattered throughout the United States and the Office of the Surgeon General can give definite answers to those questions.

What are the reasons a physician should consider participating in the Army Medical Corps Reserve Structure?

First and foremost is what I shall call the cadre system consideration. This is an amalgamation of several factors that involves dedicated groups of people who work in the system, learn how to live with it and learn to manage the system. Therefore, they are immediately available as managers when the system must be expanded rapidly. It goes without saying that our country will never go to war without medical support for the military. In almost any kind of mobilization, the total force will of necessity have to be expanded. Such an expansion would, of course, mean an increase in the total number of physicians. Physicians can be obtained in the same way as cooks and bakers and infantrymen. From a technical point of view, they would need very little training and could be put to work instantly. The biggest problem would be that of managing a large number of physicians. A cadre of managers for the Reserve would be essential.

A second reason for participation in the Army Medical Reserve can be the amalgamation of several financial considerations. The money paid for the weekend drill for most physicians, agreed, does not add up to what the ordinary physician would make during the same period of time. But the challenge is, would the physician be working that period of time anyhow? The retirement benefits after the achievement of what are called "twenty good years" has an accrued benefit over and above what the physician would place in a pension plan. My query and challenge is, would the same physician put that *much more* aside for a retirement?

Other reasons for the consideration of the Army Medical Corps Reserve include the fact that, as a physician, one is able to practice medicine and practice as he does in his civilian field. The days of sitting in a dreary armory looking at old movies on veneral disease or listening to some sergeant talk about infantry tactics are gone. Physicians in the Army Reserve who practice medicine (that is, those not in administrative positions) are truly able to practice medicine in a military setting at military and veterans hospitals.

Another consideration for the Army Medical Corps Reserve is that it can be looked upon in terms of civic duty. Most physicians become involved in community life and service during their career. Instead of working and serving with a civic club such as the Kiwanis or participating with the Red Cross, one could look at service with the Army Medical Corps Reserve in the same light as civic duty.

For many physicians Army medicine in the Reserve presents a change of pace. Additionally, there are the fellowship and new friendships that are engendered over the years. Many good doctors, nurses, and health care people are in the Army Reserve. Many of these people have other interesting avocations and personalities, and getting to know them and developing friendships that last for years is also a stimulating factor

A final factor in the consideration of participation in the Army Medical Corps Reserve is that of patriotism, pure and simple. It is truly amazing the number of people who are patriotic and behave in such a manner. Indeed I have found not a few physicians, particularly those who have some close foreign background, to feel a patriotic desire to serve this country that has granted them freedom and unexcelled opportunities.

What is service like with the Army Medical Corps Reserve? There are various levels of participation.

The first and most active is the troop program unit (TPU). The physician soldier is a member of a specific unit

organization and has a specific duty and his unit has a specific mission. Each month a weekend drill period consisting of sixteen hours during the weekend and a fourteen day period of annual training once a year is the basis of this Troop Program Unit. There are variations in the theme as to how this required duty is performed.

A second and less intense program is that of the Individual Mobilization Augmentee (IMA) in which a physician is assigned to a position in the Army Medical Corps to which he would be mobilized in the event of mobilization. The physician then spends two weeks on active duty in this particular function each year.

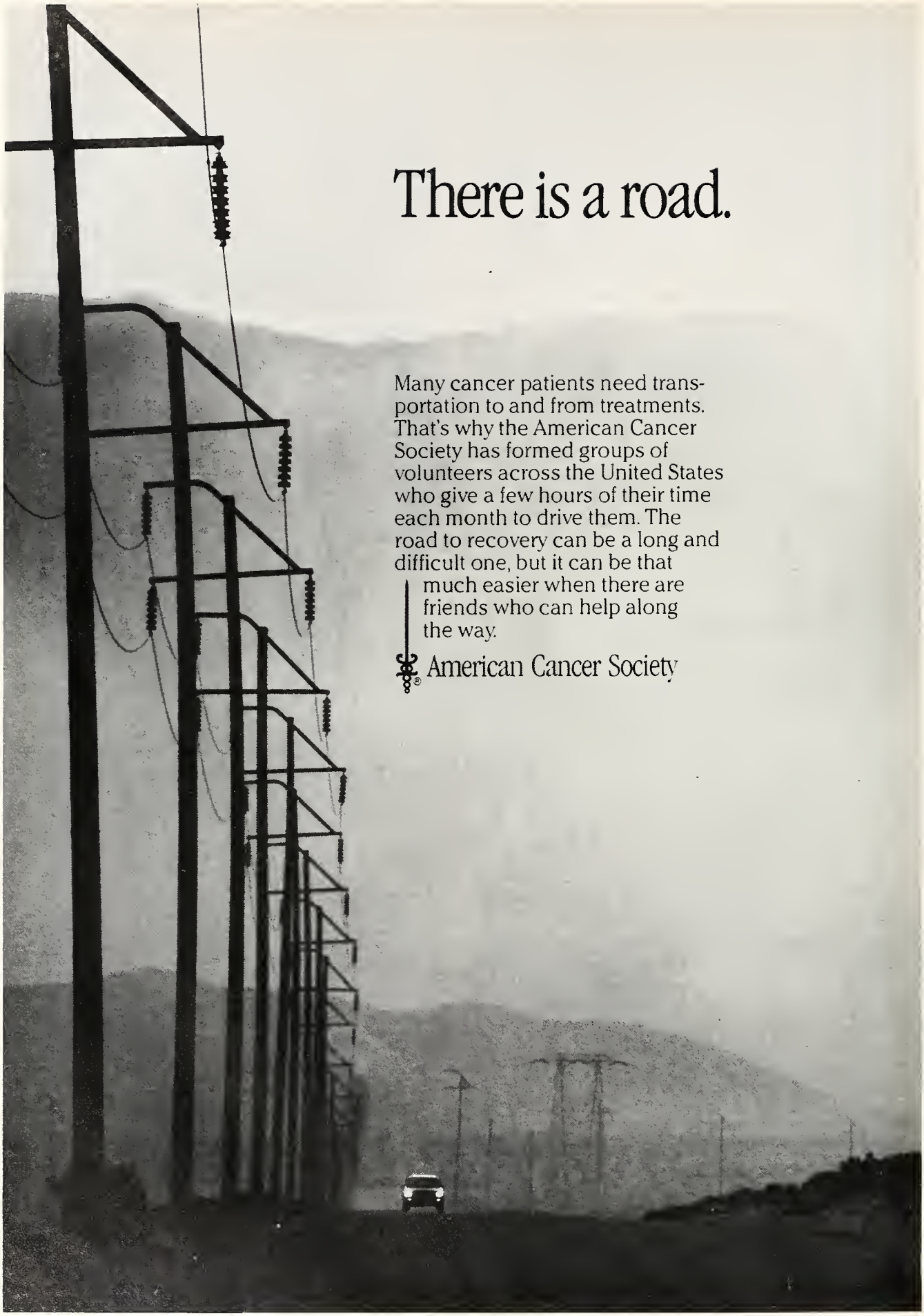
A final group is that of the Control Group in which there is minimum participation but the physician maintains his commission.

The world society we find ourselves in today is one of increasing shortages in competition for limited resources. There are multiple threats and differing global contingencies with little warning time anticipated. The national military strategy is shaped by the efforts to fulfill all these requirements of our country and today is characterized by a tremendous reliance on reserve components. The reserve components are no longer "Forces in Reserve." They are adjunct forces, fully professional, totally integrated, and completely involved. "The point has been reached where Reserves must have the same consideration as the active [components] — under most scenarios, an increasing proportion of the Reserves will mobilize, deploy and be employed along with not following the Active Army."[2]

It is to this end that a dedicated, active, and integrated Army Medical Reserve structure is an absolute necessity.

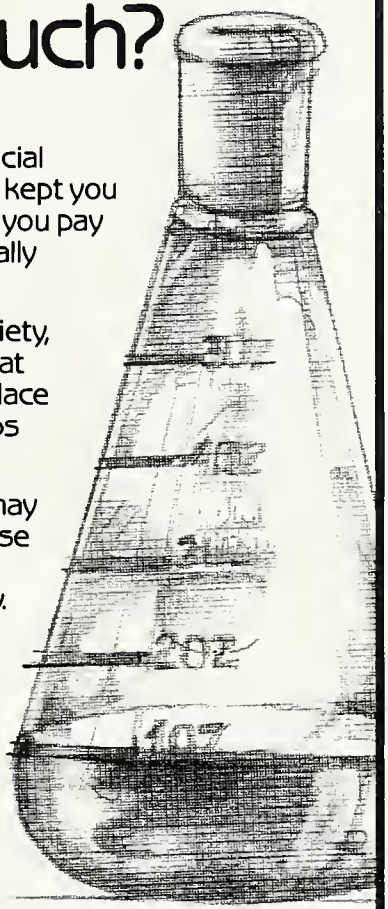
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2. Sharp BF, Skipper DB. The reserve component dilemma: Mission versus time. *Military Review*. 1984;64:62-79.



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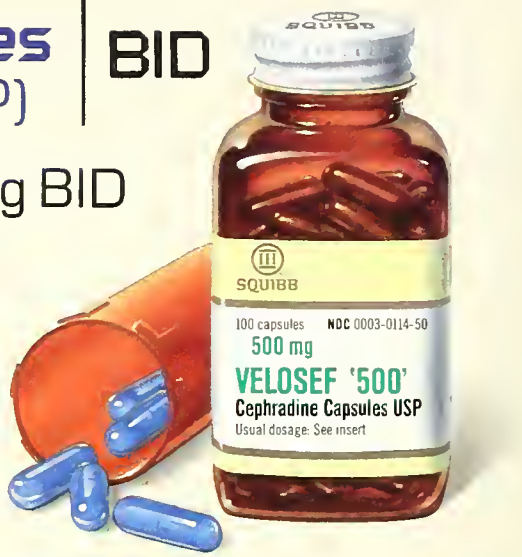
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INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli*, *P. mirabilis*, *Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

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Diuretics (potent "loop diuretics," e.g., furosemide and ethacrynic acid) — Enhanced possibility for renal toxicity.

Probenecid — Increased and prolonged blood levels of cephalosporins, resulting in increased risk of nephrotoxicity.

Drug/Laboratory Test Interactions: After treatment with cephradine, a false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®. False-positive Coombs test results may occur in newborns whose mothers received a cephalosporin prior to delivery. Cephalosporins have been reported to cause false-positive reactions in tests for urinary proteins which use sulfosalicylic acid, false elevations of urinary 17-ketosteroid values, and prolonged prothrombin times.

Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers: Since cephradine is excreted in breast milk during lactation, exercise caution when administering cephradine to a nursing woman.

Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Hematologic — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

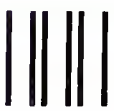
Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

For full prescribing information, consult package insert.

HOW SUPPLIED: 250 mg and 500 mg capsules in bottles of 24 and 100 and Unimatic® unit-dose packs of 100. 125 mg and 250 mg for oral suspension in bottles of 100 ml and 200 ml.

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Cefuroxime Sodium

Austin Lee, Pharm.D.

Introduction

CEFUROXIME (Zinacef-Glaxo, Inc.) is a second generation cephalosporin recently approved by the FDA for use in the United States. Since its release in the late 1970s, cefuroxime has become the most commonly prescribed cephalosporin in the United Kingdom and Europe.[1] This review will familiarize the clinician with yet another cephalosporin antibiotic. Areas to be covered include the pharmacology, clinical trials, adverse reaction profile, and dosage and administration of cefuroxime.

Chemistry and Pharmacology

Cefuroxime is a semisynthetic cephalosporin antibiotic synthesized from cephalosporin C.[1] This drug shares its 7-aminocephalosporanic acid nucleus with other cephalosporins.[2] Chemically, cefuroxime is 6R, 7R-3-carbamoyloxymethyl-7(2Z)-2-methoxyimino-(fur-2-yl)-acetamido-ceph-3-em-4-carboxylate.[1] Like other cephalosporins, cefuroxime exerts its bactericidal effect on cells by interfering with bacterial cell wall synthesis.[2, 3] It inhibits the action of transpeptidase and carboxypeptidase enzymes, which are necessary for cell wall biosynthesis, resulting in either bacterial cell lysis or filamentation.[3-5] The effects of differing inocula size, media, pH, and addition of serum on the results of *in vitro* sensitivity testing have been evaluated; the latter three factors produced no appreciable effects,[4-8] and most studies have failed to demonstrate a significant inoculum effect.[4-8] However, appreciable increases in minimum inhibitory concentrations (MIC) secondary to increases in inoculum size have occurred with some strains of bacteria.[8] Concentrations required to inhibit 90% of isolates (MIC_{90}) are listed in table 1.

Pharmacokinetics

Cefuroxime is poorly absorbed following oral administration. Urinary recovery is only 1% after a 1.0 g oral dose.[9] Therefore, cefuroxime is commercially available for parenteral use only. The manufacturer reports that development of an oral form of cefuroxime is in progress. Intravenous (IV) infusion over 30 minutes produced peak serum levels of 37.8 mcg/ml after a 500 mg dose and 51.1 mcg/ml after a 750 mg dose, whereas IV infusion of 750 mg, 1.5 and 3.0 g over 1 hour led to peak serum levels of 38.0, 64.4, and 98 mcg/ml, respectively.[10, 11] After a bolus IV injection given over a period of 3 minutes, mean peak serum concentrations were about 42-66 mcg/ml after a 500 mg dose, 53-73 mcg/ml after a 750 mg dose, and 105-151 mcg/ml after a 1.5 g dose.[9, 12-14] The apparent volume of distribution following IV injection was 9.3-12.8 L/1.73 m^2, which corresponds to the extracellular volume.[9, 15] This follows the pattern of distribution of other cephalosporins.[16] Binding to human serum protein is 33-41% and is notably less than that of other cephalosporins.[7, 9, 16] The elimination half-life generally ranges from 60-77 min.[11, 15] Urinary excretion of unaltered cefuroxime usually accounts for over 95% of each dose, and no significant metabolites have been detected.[9] Most of the dose is excreted in the first six hours, and almost all is accounted for in a 24-hour urine collection.[9, 12] Average urine levels of 500-2000 mcg/ml were present 1-2 hr after 250-500 mg, and 1000-7000 mcg/ml was present after 750 mg and 1.0 g doses.[9] Renal tubular secretion is responsible for 43-54% of cefuroxime renal elimination, as has been confirmed by administration of oral probenecid.[9]

After intramuscular (IM) injection, peak serum levels attained at 0.5-1.0 hr after administration ranged from 14.8 mcg/ml after 250 mg, 24.8-25.7 mcg/ml after 500 mg, 27-34.6 mcg/ml after 750 mg, 32.2-40 mcg/ml after 1.0 g, to 46 mcg/ml after 1.5 g.[9, 13, 17] Serum concentrations were maintained at detectable levels for 8 hours at all dosages except the 250 mg dose.[9] The serum half-life ranged from 65 to 82 min.[9] Mean urinary recovery was at least 95% of the dose.[9] The total amount of drug available is the same for equivalent doses given IM or IV based upon

Table 1
Concentrations Required to Inhibit 90% of Isolates (MIC_{90})[5, 6, 8]

Organisms	Cefuroxime mcg/ml	Cefamandole mcg/ml
S. aureus (unspecified)	0.8-1.6	0.2-0.8
S. epidermidis	0.12-4.0	0.12-2.0
S. faecalis	> 64	> 32
S. pneumoniae	0.006-0.01	0.03-0.06
N. gonorrhea	0.12-0.25	1-2
H. influenzae	0.25-0.5	0.25-0.5
E. coli	6.2-12.5	6.2-12.5
Klebsiella spp.	1.6-3.1	12.5-25
Enterobacter spp.	200-400	200-400
Citrobacter spp.	6.2-12.5	< 0.8
Providencia spp.	200	100
Proteus spp.		
Indole-negative	1.6	3.1
Indole-positive	> 400	25-100
Pseudomonas spp.	16- > 32	32-> 32
Serratia spp.	> 400	> 400
Acinetobacter spp.	> 400	200-400
B. fragilis	> 64	16-32

From the Department of Pharmacy, Duke University Medical Center, Durham 27710.

area under the concentration-time curve.[9] Cefuroxime distributes into many body tissues and fluids.[3] Numerous studies in neonates, children, and adults with meningitis have documented its penetration into cerebrospinal fluid (CSF). Penetration has correlated with the degree of meningeal inflammation.[18, 19] The mean CSF levels in these studies have ranged from 2.4 to 10.3 mcg/ml and have been considered adequate for treatment of meningitis caused by susceptible pathogens.[18, 20-25]

Elderly Patients. A pharmacokinetic study conducted in 40 elderly patients (mean age 77.5 years) concluded that dosage and dosage intervals should depend upon renal function rather than upon age.[26] Therefore, the guidelines for dosing in the normal adult patient should be followed.

Neonates and Infants. Neonates less than 3 weeks old (average 4.2 days) exhibited a half-life of approximately 275 minutes after a 10 mg/kg IM dose.[20] The half-life was age-related and ranged from 240 minutes in 14 day-old to 338 minutes in 1 day-old infants. Peak serum levels ranged from 18.6 to 25.6 mcg/ml and showed a slight dependency on body weight. Urine excretion accounted for 53-87% of each dose and urine levels were 10-fold greater than serum levels. Multiple 10 mg/kg doses given every 8 hours showed no evidence of drug accumulation if body weight was greater than 2,000 g. The investigators suggested twice-daily dosing with body weight less than 2,000 g. Another study observed a similar age dependency for cefuroxime elimination, with the half-life decreasing from 5.1 hr on day 1 of life to 1.9 hr on day 6 in neonates of greater than 2.5 kg birthweight.[27] Neonates of less than 2.5 kg birthweight excreted cefuroxime more slowly. Mean peak serum levels ranged from 19.1 to 24.5 mcg/ml after 15 mg/kg and from 39.6 to 56.7 mcg/ml after 25 mg/kg IM doses. These investigators also suggested a twice-daily dosing schedule in neonates with birthweight less than 2.5 kg. Infants and children aged 3 weeks to 2 years (average 6.5 months) and ranging in weight from 2,800 to 9,500 g (average 6,500 g) were also studied.[28] After a 15 mg/kg IM dose, the peak serum level was 26.6 mcg/ml at 0.5 hr with a serum half-life of 63.8 min. Intravenous administration of 12 mg/kg produced a peak serum level of 30 mcg/ml. Half-lives in these older children were similar to those observed in adults.

Patients with Impaired Renal Function. Cefuroxime excretion is reduced by renal failure. Half-lives have been determined for varying degrees of creatinine clearance (Cl_{cr}), (see table 2). Cefuroxime levels achieved in peritoneal dialysate ranged between 15 and 20 mcg/ml.[29] Cefuroxime has been added to peritoneal dialysate of patients on continuous peritoneal dialysis in a final concentration of 200 mg/L for 6 cycles/day.[30] The mean dialysate level was 26 mg/L in effluent and 18 mg/L in serum at the end of the first exchange. Dosage guidelines for cefuroxime are based upon the fact that significant accumulation does not occur until Cl_{cr} is less than 20 ml/min.[31] Dosing guidelines based upon Cl_{cr} are listed in table 3. Patients on hemodialysis should receive a 500 mg loading dose post-dialysis.[32]

Table 2
Determination of Cefuroxime Half-life ($t_{1/2}$) Based upon Creatinine Clearance (Cl_{cr})[29]

Cl_{cr}(ml/min)	$t_{1/2}$ (hours)
> 80	1.05
50-79	1.03
25-46	2.55
10-24	5.05
< 10	14.8
anuria (no dialysis)	21.9
on hemodialysis	3.75
on peritoneal dialysis	13.6

Table 3
Cefuroxime Dosing Guidelines Based Upon Creatinine Clearance (Cl_{cr})[3]

Cl_{cr}(ml/min)	Dose	Frequency
> 20	750 mg-1.5 g	q8h
10-20	750 mg	q12h
< 10	750 mg	q24h

Clinical Trials

The Food and Drug Administration has approved the use of cefuroxime for the treatment of serious infections caused by susceptible strains of specific microorganisms in the following diseases: 1) lower respiratory infections, 2) urinary tract infections, 3) skin and skin structure infections, 4) septicemia, 5) meningitis, and 6) uncomplicated gonorrhea and disseminated gonococcal infections.[3] Few published comparative trials are available for evaluation of cefuroxime. Most of the available clinical data are derived from non-comparative open trials designed to evaluate the safety and efficacy of cefuroxime.

Lower Respiratory Tract Infection. Cefuroxime's antibacterial spectrum encompasses *S.pneumoniae, H. influenzae, S. aureus,* and *Klebsiella* sp., the bacteria most likely to cause pneumonia. Furthermore, because of its stability to the beta lactamases of *S. aureus* and *H. influenzae,* it provides a broad coverage for pneumonia. Two large non-comparative trials (total 464 patients) have assessed cefuroxime 750-1000 mg IM q8h for lower respiratory tract infections.[34, 35] The response rates were 88-90% for bronchopneumonia, 89-97% for exacerbation of COPD, 69% for postoperative pneumonia, 86% for bronchitis, and 86% for pneumonia secondary to cancer obstruction. Other non-comparative studies of cefuroxime in the treatment of adult respiratory tract infection have revealed cure rates ranging between 90-100% after regimens of 750 mg-1.5g IM or IV q8-12h.[36-38] Cefuroxime 25 mg/kg IV or IM q8h has also been an effective treatment for pneumonia in 100 infants and children.[39] Dosages of 15 mg/kg q8h and 50 mg/kg q12h have provided adequate response in two other smaller trials in children.[40, 41]

Bone and Joint Infections. Data on clinical efficacy of cefuroxime in bone and joint infections are limited. In a series of 75 children with suppurative bone and joint infections, patients received either cefamandole or cefuroxime as their initial antimicrobial therapy.[42] Twenty-seven children received cefuroxime in doses of 15 mg/kg/day in three

divided doses. Parenteral therapy was administered for a mean duration of five days (range 2-21 days). Therapy was completed with oral antibiotics, in most cases with either cefaclor or cephalexin. All patients showed clinical improvement while receiving cefuroxime, although one treatment failure was reported.

Cefuroxime may potentially be effective in the treatment of osteomyelitis and septic arthritis. However, its definitive role in these conditions has yet to be established and will require clinical trials with long-term follow-up for sequelae.

Gonorrhea. Lossick et al compared a single IM dose of 1.5 g of cefuroxime with 4.8 million units of procaine penicillin G, both combined with 1.0 g of oral probenecid.[43] Overall response was 96% for cefuroxime and 95% for penicillin. Similar success has been reported in non-comparative studies after treatment with 1.0 and 1.5 g cefuroxime with or without probenecid.[44, 45] Cefuroxime has been shown to have *in vitro* activity against beta-lactamase-producing strains of gonococci.[8] Cefuroxime has been used as a single 25 mg/kg IM dose in the treatment of gonorrhea in children with pharyngeal, rectal, and/or urethral disease.[46] Seventy-six percent were cured completely within 48 hours after treatment. The remainder had persistence of symptoms due to concurrent chlamydial infection.

Although a single dose of cefuroxime has proven effective in the treatment of uncomplicated gonococcal infection, it should be reserved for patients either allergic to penicillin or known to have strains of *N. gonorrhoeae* that produce beta-lactamase.

Meningitis. Ampicillin and chloramphenicol are currently recommended for initial therapy of bacterial meningitis in children. The emergence of ampicillin- and chloramphenicol-resistant strains of *H. influenzae* has stimulated the search for alternative forms of antibiotic therapy. The overall performance of first and some second generation cephalosporins in bacterial meningitis has been poor. A review by Gold et al of the results of studies on the degree of penetration of cefuroxime into the CSF in various disease states concluded that 1) the degree of CSF penetration of cefuroxime generally increases with the degree of meningeal inflammation, and 2) the degree of penetration is somewhat variable and shows no clear relationship to the time interval between antibiotic administration and sampling of the CSF.[2] Friedrich et al concluded that cefuroxime, like earlier cephalosporins, diffuses poorly into the CSF.[47] However, several reports have documented the efficacy of cefuroxime in the treatment of meningitis in adults and children.

A study conducted by a Swedish collaborative group supports the potential role of cefuroxime in the treatment of meningitis.[25] In a prospective, randomized study these investigators compared cefuroxime (60-75 mg/kg/dose q8h in 9 children, 3 g q8h in 11 adults) with a combination of ampicillin and chloramphenicol in 40 evaluable patients with culture-proven bacterial meningitis. Clinical isolates included *H. influenzae* (20), *N. meningitidis* (11), *S. pneumoniae* (5), *B. cattarhalis* (1), *S. aureus* (1), alpha-streptococcus (1), and *H. parainfluenza* (1). The response rates of 86% for cefuroxime and 74% for ampicillin-chloramphenicol were not statistically different, indicating that cefuroxime was at least as effective as combination therapy in this study.

Cefuroxime is approved for use in the treatment of bacterial meningitis.[3] Because of more potent antimicrobial activity and increased diffusion into the CSF, the third generation cephalosporins show greater promise for the treatment of meningitis than do the first two generations.

Urinary Tract Infection. Cefuroxime (which is a parenteral antibiotic) will probably have little role to play in the outpatient treatment of urinary tract infections. Hofstetter et al reported clinical cure or improvement in 21 of 26 patients treated with cefuroxime 2.25 g IV daily.[48] Fifteen of 29 strains of bacteria were eradicated. In a study of 40 patients (21 of whom had underlying urological conditions), 38 of the 40 original pathogens isolated were eradicated.[49] Treatment consisted of cefuroxime 500 mg IM q8h.

Hospital acquired infection in 34 geriatric patients with recurrent or chronic urinary tract infection was treated with cefuroxime 500 mg IM or 750 mg IM given three times a day for 7 days.[50] The original pathogen was eliminated in 7 of 16 treated with 500 mg doses and in 13 of 18 given 750 mg doses. Following treatment with cefuroxime 2-4 g daily, 14 of 22 patients achieved cures after having failed on other antibiotics.

Soft-Tissue Infections. Cefuroxime has proven effective in treating soft-tissue infections. Fifty-five children with soft-tissue infections were treated with cefuroxime.[51] Most children were treated with 50 mg/kg/day IV in 4 divided doses. Clinical results were good in 50, fair in 2, and unevaluable in 3. Adult doses of 750 mg every 8h and pediatric doses of 50 mg/kg/day divided into 3-4 doses should be used when the etiologic agent is a susceptible organism.[3] When the pathogen is almost certainly limited to gram-positive aerobic organisms, an antibiotic with a more narrow spectrum of activity should be used.

Bacteremia. Clinical studies have included small numbers of septic patients who have been successfully treated with cefuroxime.[52, 53] Cefuroxime was used for empiric coverage in 57 children with leukemia or solid tumor who developed fever while neutropenic.[54] The combination of cefuroxime plus gentamicin was effective in all cases. However, a list of pathogen and sensitivity data is absent; therefore, the merits of cefuroxime in this setting are questionable.

Surgical Prophylaxis. Cefuroxime's ability to achieve significant concentrations in most body fluids and tissues has provoked interest in its use for surgical prophylaxis. Cefuroxime provided effective prophylaxis in 69 total hip and 37 total knee replacements.[55] Patients received three 1 or 1.5 g IM doses at the time of surgery and 6 and 12 hours later. Comparison of cefuroxime and placebo in coronary artery bypass surgery showed no difference in the incidence of sternal or leg wound infection.[56] However, significantly fewer cefuroxime-treated patients developed postoperative pulmonary infection. This study has been criticized for the vague clinical criteria used to define complications; therefore, interpretation of the results is limited.

In upper gastrointestinal surgery, patients receiving a single 1.5 g IV dose of cefuroxime prior to upper GI

surgery showed a significant reduction in wound sepsis, abscess and septicemia when compared with controls.[57] Cefuroxime 1.5 g IV was used with or without metronidazole and also compared with placebo in rectocolonic, gastric, and small bowel surgery.[58] Cefuroxime-treated patients developed fewer infections compared with placebo, and more infection when compared with combination therapy. Cefuroxime was significantly better than placebo in prevention of infection after small bowel and gastric surgery. One study included 416 patients with acute cholecystitis and compared the prophylactic efficacy of three cephalosporins in preventing wound infections.[59] Patients received either 1 g cefazolin, 0.75 g cefuroxime or 1 g of cefamandole. The degree of decrease in wound infection rates with cefuroxime was not significantly better than that achieved with cefazolin or cefamandole. In a randomized double-blind study of 472 patients undergoing major elective gynecologic surgery, one group of patients received a single postoperative 1.5 g dose of cefuroxime, and the others received no antibiotics.[60] Results suggested that a single dose of cefuroxime reduced the frequency of postoperative pyrexia, urinary tract infections, and amount of antibiotic needed after surgery. However, cefuroxime's role in gynecologic prophylaxis may be hindered by its limited *in vitro* activity against *B. fragilis*. A combination of metronidazole and cefuroxime was associated with no postoperative wound infection in total abdominal hysterectomy, vaginal hysterectomy, pelvis floor repair, or salpingectomy.[61] Cefuroxime 1.5 g IV was compared with placebo for prophylaxis prior to transurethral resection of the prostate.[62] No urinary tract infections were reported for either group postoperatively.

Side Effects and Toxicity

Cefuroxime is well tolerated by adults and children. The most frequently encountered side effect is local irritation at the site of injection, which includes thrombophlebitis and transient pain after intramuscular injection.[3] Pain after intramuscular administration may be lessened by co-administration of lidocaine.[44] Rash, pruritis, urticaria, and positive Coombs test have been relatively uncommon.[3] Caution is advised when administering this agent to patients with prior allergic reactions to other beta-lactam antibiotics.[3] Gastrointestinal reactions such as stomatitis, nausea, and diarrhea occur infrequently. Transient elevations in liver enzymes are the most frequent laboratory abnormalities, but these have been clinically inconsequential. Clinical deterioration of renal function has not been observed, although elevations in blood urea nitrogen (BUN) have been reported. Patients with pre-existing renal disease have been treated successfully with cefuroxime with no apparent deterioration in renal function.[63] Hematologic abnormalities such as decreases in hemoglobin and hematocrit, eosinophilia, leukopenia, and neutropenia have been observed occasionally.[3] Pseudomembranous colitis, disulfiram reaction, and bleeding tendencies have not been reported during cefuroxime therapy.

Drug Interactions

The effects of oral administration of probenecid 500 mg 2 hours before and again 1 hour after IM injection of cefuroxime were studied in a cross-over study in 6 volunteers.[9] Concomitant probenecid increased serum concentration (30%) and serum half-life (32%), and decreased

Table 4
Dosage Guidelines for Cefuroxime Treatment[3]

Type of infection	Usual recommended dose
Adults (over 12)	
Uncomplicated UTI Skin and skin structure infection Uncomplicated pneumonia Disseminated gonorrhea	750 mg q8h IM or IV
Severe or complicated infections	1.5 g q8h IM or IV
Life-threatening infections Infections due to less-susceptible organisms	1.5 g q6h IV
Bacterial meningitis	up to 3.0 g q6h IV
Prophylactic use in clean-contaminated or potentially contaminated surgical procedures	1.5 g IV 30 to 60 min before initial incision, followed by 750 mg q8h IM or IV in prolonged procedures
Uncomplicated gonorrhea	1.5 g IM given as a single dose at two different sites, together with 1.0 g oral probenecid
Patients with renal insufficiency	See table 3
Infants and children over three months	
Mild to moderate infections	50 to 100 mg/kg/day in equally divided doses q6-8h
Severe or serious infections	100 mg/kg/day (not to exceed the maximum adult dose)
Bacterial meningitis	initially 200-240 mg/kg/day IV in divided doses q6-8h; may be reduced to 100 mg/kg/day IV on clinical improvement
Patients with renal insufficiency	modify frequency of dosage consistent with the recommendations for adults

apparent volume of distribution (20%) and renal clearance (40%).

Dosage and Administration

The usual dose of cefuroxime for urinary tract, lower respiratory tract, and skin and soft tissue infection of mild to moderate severity is 750 mg IM or IV q8h.[3] The dosage for severe infection of the urinary tract, respiratory tract, skin and soft tissue, and for sepsis is 1.5 g IM or IV q8h.[3] Life-threatening infections, including meningitis, are treated with 3 g IV q8h. A single 1.5 g IV dose immediately before surgery is recommended when cefuroxime is used for surgical prophylaxis.[3] A single 1.5 g IM dose plus 1 g of oral probenecid is efficacious in the treatment of gonorrhea.[3] In children more than 3 months old the usual dose is 50-100 mg/kg/day in equally divided doses, usually every 6-8 hours; however, initial doses of 200-240 mg/kg/day are recommended for meningitis therapy[3] (refer to tables 3 and 4 for general dosing guidelines and for patients with renal dysfunction). Cefuroxime may be given IV or by deep IM injection into a large muscle mass.[3] The IV route may be preferable for patients with bacterial septicemia or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.[3] Intravenous injections may be given over 3-5 minutes as a bolus or as an infusion.[3] Cefuroxime is stable in most standard dextrose and saline solutions.[3] Solutions of cefuroxime, like those of most beta-lactam antibiotics, should not be added to solutions of sodium bicarbonate or aminoglycosides because of potential drug inactivation.[3] Cefuroxime has also been found compatible for 24 hours at room temperature when admixed in IV infusion with heparin (10 and 50 units/ml) in 0.9% NaCl injection, and KCl (10 and 40 mEq/L) in 0.9% NaCl injection.[3] As with other cephalosporins, however, cefuroxime solutions and suspensions tend to darken depending on storage conditions, without adversely affecting drug potency.[3]

Availability and Cost

Cefuroxime is available in 750 mg and 1.5 g vials. The average wholesale price is $5.88 and $11.70, respectively.[64]* At the Duke University Medical Center, daily patient cost is similar or lower for cefuroxime therapy when compared with cefamandole and cefoxitin (when comparisons are based upon manufacturer's recommendations for moderate-severe and life-threatening infections).

Summary

Cefuroxime is a new beta-lactamase-stable cephalosporin with a second generation antimicrobial spectrum similar to that of cefamandole. This new agent is efficacious and offers certain advantages over cefamandole. Cefuroxime has the advantage of a longer dosing interval (q8h), lack of bleeding abnormalities, usefulness in pediatric infections, long history of experience in Europe, and possibly a lower cost for therapy.

References available from the NCMJ editorial office.

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Pericardial Pseudoeffusion Due to Steroid-Induced Lipomatosis

Cynthia D. Mulrow, M.D. and G. Ralph Corey, M.D.

A chest radiograph showing cardiomegaly, a "water bottle" heart or the epicardial fat pad sign usually connotes a pericardial effusion. In recent years ultrasonography has been used to confirm this diagnosis. Unfortunately, echocardiography cannot differentiate between fluid and adipose tissue. We present a case of suspected pericardial effusion in which an awareness of the possibility of steroid-induced intrathoracic lipomatosis would have led to computerized tomographic scanning and prevented surgical exploration.

Case Report

A 47-year-old man developed a pruritic, eczematous rash on his left lower leg after taking hydrochlorothiazide for mild hypertension. Despite stopping the thiazide, the rash progressed; systemic steroids were used and the rash improved. Over a six month period multiple attempts to taper the steroids resulted in severe flares of the rash, and the patient was admitted for evaluation.

Serological tests for collagen-vascular disease, venography, and computerized tomographic scans of the abdomen and left lower leg were negative. When we decreased the steroid dose the patient developed nausea, dyspnea, and tachycardia. While breathing room air his arterial pH was 7.50, pCO_2 23 mm Hg, and pO_2 65 mm Hg. His chest radiograph (figure 1) revealed cardiomegaly and a prominent mediastinum. A ventilation perfusion lung scan was negative.

Diuretics (given for presumed volume overload) resulted in a blood pressure drop from 140/90 to 110/80 and a rise in pulse rate from 100 to 130. He had a pulsus paradoxus of 18 mm Hg. He stabilized when given fluids.

An echocardiogram (figure 2) was interpreted as showing a large pericardial effusion and a thick pericardium with "stranding" suggestive of a malignant process. A diagnostic pericardiectomy was undertaken but no pericardial effusion was found; the pericardium appeared normal except for an unusually large amount of pericardial fat. Pathological examination revealed normal pericardium with excessive but normal adipose tissue. The patient recovered from surgery without complications. The steroids were eventually tapered without recurrence of the rash. The etiology of his rash and systemic symptoms was never firmly established.

From the Division of General Internal Medicine, Duke University Medical Center, Durham 27710.

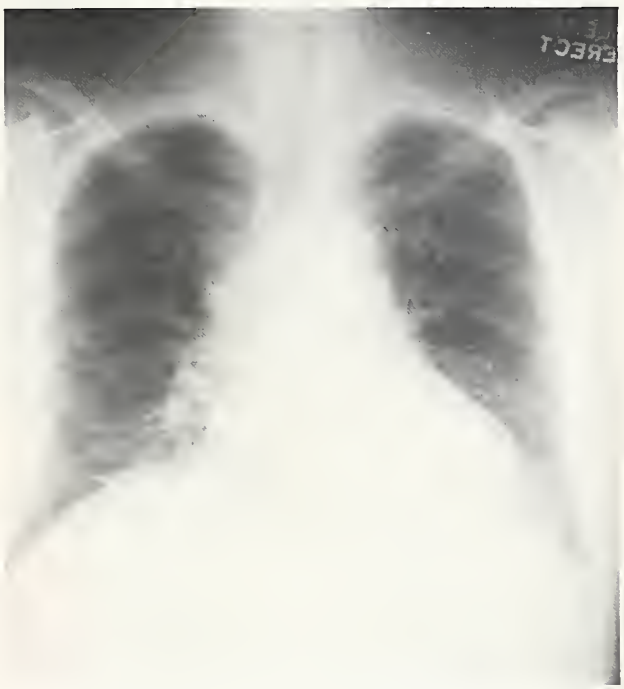


Figure 1. *Chest radiograph revealing cardiomegaly and a prominent mediastinum.*

Discussion

Increased truncal fat deposits, including intrathoracic fat deposits, occur in patients with endogenous[1] or exogenous[2] steroid excess. Most patients have other clinical characteristics suggestive of Cushing's syndrome, but it is sometimes difficult to distinguish pericardial fat deposition from more serious conditions such as neoplastic effusions. A history of long-term steroid use (usually more than 30 mg prednisone daily) is helpful. Excess fat may be noted in truncal, facial and supraclavicular areas. Chest radiographs commonly reveal symmetrical mediastinal enlargement, but pericardiac masses and generalized enlargement of the cardiac silhouette can be seen. The fat shadows are often poorly defined and not as dense as other superior mediastinal masses such as thymoma or lymphoma. Compression effects on the trachea or ribs are not seen.

Diagnosis of mediastinal lipomatosis depends on clinical suspicion, the use of computerized tomographic scanning[3] and occasionally on invasive procedures such as needle biopsy or thoracotomy. However, in patients with presumed pericardial effusion, echocardiography is the most

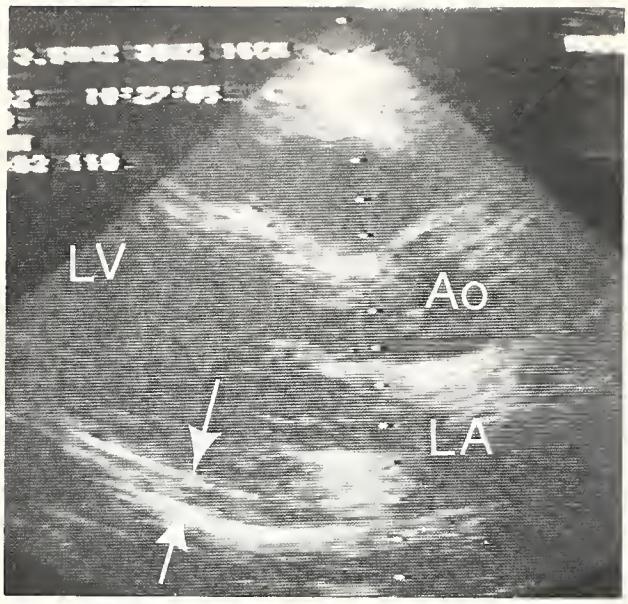


Figure 2. *Left parasternal long axis echocardiogram showing pericardial effusion (between arrows). Ao = Aortic root; LV = Left ventricle; LA = Left atrium.*

commonly used noninvasive diagnostic tool. Known drawbacks to this procedure include false positive diagnoses of pericardial effusions in patients with pericardial neoplastic disease.[4]

Our patient had a pericardial pseudoeffusion secondary to corticosteroid-induced pericardial fat deposition. Although pericardial pseudoeffusion is not a common occurrence, computerized tomography can usually distinguish low density adipose tissue from pericardial fluid or higher density tissue such as myocardium or tumor.[4] In particularly difficult cases tissue biopsy may be necessary.

Since increased cardiac and mediastinal adipose tissue does not appear to cause clinical dysfunction, there is generally no need for therapy.[2] Excess adipose tissue regresses after removal of the steroid stimulus.

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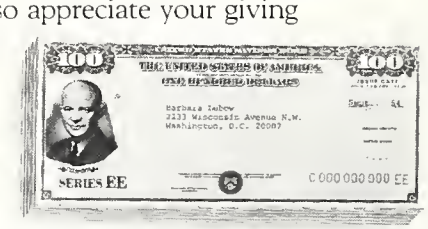


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IN STATE

March 13

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March 20

Pulmonary Embolism — Acute Care and Prevention
Place: Sanford
Credit: 2 hours Category 1 AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

March 21-22

Current Cancer Research — Springboards for the Future
Place: Chapel Hill
Credit: 10 hours Category 1 AMA-PRA
Info: Pam Upchurch, Lineberger Cancer Research Center, UNC, Chapel Hill 27514. 919/966-3036

April 2

Physicians, Their Families and Stress — How to Survive in 1985
Place: Greensboro
Info: David M. Kaplan, M.D., P.O. Box 220, Summerfield 27358.

April 11

The North Carolina Neuro-Ophthalmology Review
Place: Chapel Hill
Credit: 4 hours Category 1 AMA
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April 13

Neurosciences Update
Place: New Bern
Info: William B. Hunt, Jr., M.D., Box 2157, New Bern 28560. 919/633-8607

April 15-June 7

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April 17

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April 27

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May 1

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May 3-4

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March 16

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March 29-31

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In Memoriam

Robert Wefer Williams, M.D.

Dr. Robert Wefer Williams died December 15, 1984 in Wilmington after a long illness. He was born in New York City on January 27, 1921, the son of Elsie Wefer and Robert Jay Williams. After graduating from Phillips Exeter Academy and Harvard College, he attended Cornell University Medical College, graduating in 1945. He was an Army-Air Force Flight Surgeon in occupied Germany from 1946 to 1948.

Following his honorable discharge as a Major from the Air Force in 1948, he worked at the Strang Clinic of New York Memorial Hospital. He then served a surgical residency at the Bowman Gray Medical School. Practicing as a general and thoracic surgeon in Wilmington from 1953 to 1978, he was especially recognized for his surgery on infants and children, much of which was done at the Babies Hospital in Wrightsville Beach.

Dr. Williams was a Fellow of the American College of Surgeons, a diplomate of the American Board of Surgery, and an early diplomate of the American Board of Thoracic Surgery.

He is survived by his wife, Isabel Martin, whom he married in 1943, four children, and seven grandchildren.

News Notes

The **North Carolina Board of Medical Examiners** reminds our members that anyone representing himself or herself as a physician assistant must be approved to perform medical acts by the Board of Medical Examiners of the State of North Carolina. Further, the Board advises that the initials "P.A." stand for "physician assistant" and any individuals who identify themselves in this fashion should be thoroughly familiar with the General Statutes of the State of North Carolina, particularly section 90-18.1.

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Letters to the Editor

Religion and Medicine

To the Editor:

I would first like to applaud the article "Thoughts on the beliefs of religious and medical institutions" by Dr. Albert Warshauer in the January issue of NCMJ (1985;46:29-32). The article presents a brief but thought provoking and thoughtful discussion of a number of practical as well as ethical problems of medical practice today. I would suggest not only practitioners but medical students as well should read and digest this excellent communication.

I am especially concerned with problem number 4 in the article, namely blood transfusion as it applies to the Jehovah's Witness patient. Dr. Warshauer has written a very good summary of my own personal feelings regarding this particular problem. Additionally, his summary in number 9 on medical fees and malpractice awards is a very good summary of the problem.

I disagree however on the role of the physician in regard to some of the social-political areas such as the Vietnam war, civil rights, and more recent problems of drought and areas of famine. Some of these problems are natural, which none of us have control over. Some are political and I do not deny that physicians should have political involvement, but the problem is much larger than we, representing 0.4% of the population of the United States, could hope to accomplish. In regard to promoting the use of seat belts, I think that the medical profession has tried; however, the general population just does not seem to be interested. To use an old cliche, "you can lead a horse to water but you can not make him drink."

By the way, does anyone know of a physician who is a Jehovah's Witness?

Again, my thanks for a very interesting, timely, and thought provoking article.

Lloyd F. Redick, M.D.
Department of Anesthesiology
Duke University Medical Center
Durham 27710

Several physicians responded to the February 1985 Physicians' Forum question about patients who refuse lifesaving treatment, among whom Jehovah's Witnesses may be counted (NCMJ 1985; 46:89-92).

CORRECTIONS

In the article "Common Mononeuropathies" by E. Wayne Massey, M.D., published in the January 1985 issue of the NCMJ, figures 5 and 8 were inadvertently switched. Plates 1 through VI were reprinted with the permission of the publisher, W. B. Saunders Company, from Haymaker and Woodhall, *Peripheral Nerve Injuries*.

In the article "Interactions Between Digitalis and Antiarrhythmic Drugs" by Thomas L. Wenger, M.D. and Harold C. Strauss, M.D., C.M., published in the January 1985 issue of the NCMJ, figures 1 and 2 were reprinted with permission from Leahey EB Jr, Reiffel JA, Giardina EGV, Bigger JT Jr. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. A prospective study. Ann Int Med 1980;92:605-8.

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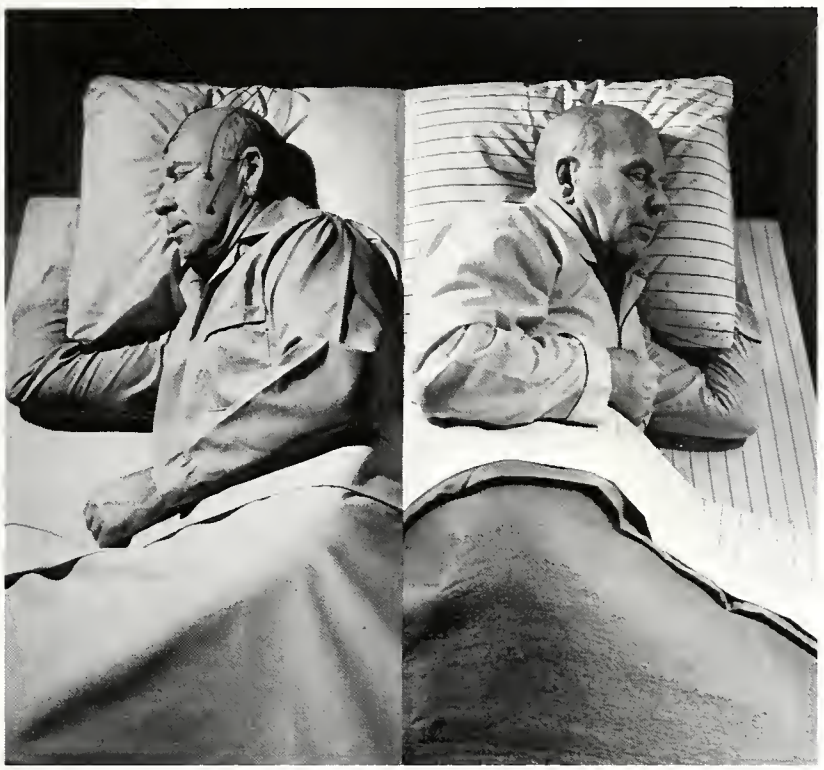
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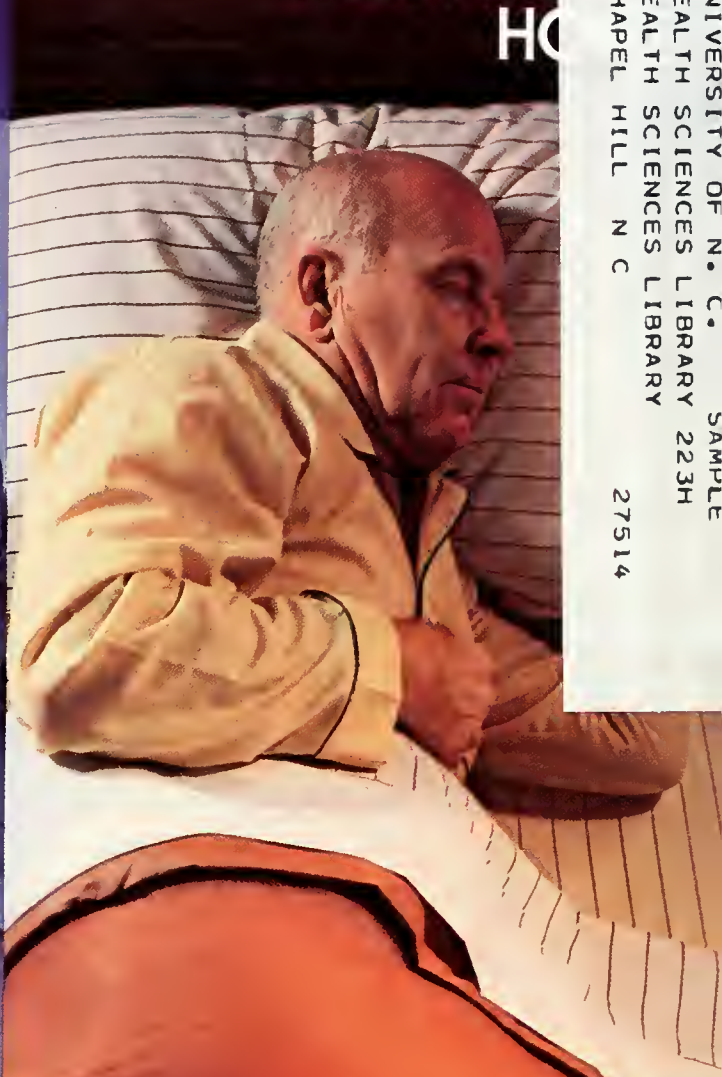
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A young woman with a fatal illness and a strong desire to truly live each day until her last causes the staff of a coronary care unit to rethink and, in the end, restructure their treatment of terminal patients. page 197

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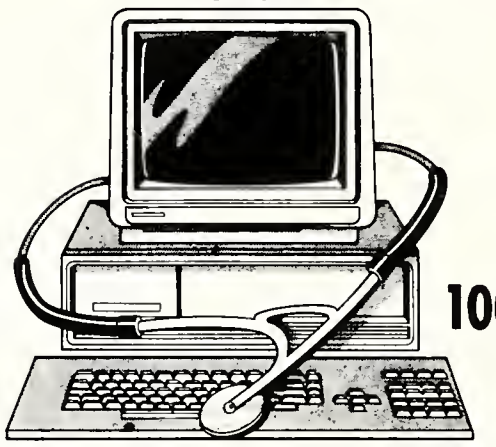
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Meetings Scheduled

Notice to: Delegates, Alternate Delegates, Officials of the North Carolina Medical Society, and Presidents and Secretaries of county medical societies.

Sessions of the HOUSE OF DELEGATES will convene in the Cardinal Ballroom, Pinehurst Hotel, Pinehurst, North Carolina, at the following times:

Thursday, May 2, 1985 — 10:00 a.m. — Opening Session
Saturday, May 4, 1985 — 2:00 p.m. — Second Session

A member of the CREDENTIALS COMMITTEE will be present at the Desk in the Hotel Lobby, Wednesday, May 1, 1985, 3:00 p.m. to 5:00 p.m., and Thursday, May 2, 1985, 8:30 a.m. to 10:00 a.m. to certify Delegates. Delegates are urged to bring their Credential Cards for presentation at the Registration Desk. Delegate Badges must be worn to be seated in the HOUSE OF DELEGATES.

REFERENCE COMMITTEE HEARINGS

Reference Committee hearings are scheduled to begin Thursday, May 2, 1985, at 2:00 p.m.

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EDITORIAL

Short Term Goals for Young Health Care Providers

Donald D. Neish, M.D.

I'M no wordsmith with the skills of a Lewis Thomas, but the Lives of My Cells may have enough experience for me to qualify as Sage for my son, The Medical Student, my daughter, The Nurse and all of their friends who have chosen to become Health Care Providers. What a crass designation that is!

My loved ones, their friends, and I are stretching ourselves to the limit each day, laboring for the strangers we meet and treat as patients — sorry, clients. These distressed humans, who are sick, don't remain strangers to us very long, because we soon begin to serve them in the finest tradition of caring for The Consumer of Health Care as outlined years ago by Dr. Francis Peabody. (The secret in caring for patients is to care for the patient.)

The Medical Student visits. Not wanting to go through the rigors of medical school again myself, I'm relieved that he drops in only on occasion, his mission a good meal, to do laundry, or to ask the old man how he got through medical school in the Fifties. I allow it may have been easier then, because we did not have to deal with the explosion of knowledge now extant.

Being blasted by the anatomy and biochemistry his first year has not burned out the caring part of him. He cares for the patients that first year med students are allowed to interact with, cares for his classmates, who are stressed more than at any time during the pre-med days. He cares for himself, is amazed how the pressures build up and cause even healthy young bodies to cry out in pain when pushed too hard.

What can I say to him when he hurts? I remember my first year in medical school, the panic, the grinding fatigue, the dragging out of bed in the morning to face another impossible day. Yet, I can see my old self in his eyes and in what he says. He loves the challenge of his chance to acquire new and exciting medical knowledge. He hopes he can put it all to good use some day, at the research bench, or the bedside, because he cares for people.

Regardless of what the for-profit corporate medical plans, the Feds, the lawyers, or an envious public do to us, they will never be able to take our caring away from us. Neither can we be bored for very long, because new things will stimulate us to be students of the human condition for the rest of our professional lives.

So, I convey to him as best I can: 1) You picked it son, and you and your friends will have to learn to cope with it all, each in your own way. 2) I'm confident you will survive, as I did. You have better maturity and skills than I had at your age. 3) You love it. Admit it. That will keep you going during the rough times.

I take a phone call from The Nurse. Like her brother, she chose her profession with my blessing, but not my pressure. After getting her degree, she could have picked some laid-back office job, but no, there she is in the Teaching Hospital, working those shifts that cause the body's biologic clock to protest: cruel and unusual punishment. She cares, and the hospital staff sees that, the patients and families warm to it. Professionalism and caring, that is where she gets her daily worthwhiles.

She and I get to see the house staff Providers and how they are knocked about. All the old intern and resident problems I remember are still there, even though the participants are renamed PGY-1s or some such. There are the frustrations, the sleep deprivation, the highly charged contacts with patient, family, attendings — the daily confrontations with vulgarity and death.

I feel for you, Young Health Care Providers. I was almost a pediatrician myself once; now I do a fair bit of geriatrics, but I feel for those pediatric house officers. In my practice, I have to deal with all those over-the-shoulder-watchers who wish to tell me the best way to handle the last days of terminal aging. I can hardly believe the recent prediction that I may live to see the controversy rise to such a pitch that there will be "Granny Doe" legislation to contend with.

In addition to "Baby Doe," the pediatrician faces many new snares and delusions. One of Walt Kelly's POGO characters said, "We have met the enemy and they is us." Is that an explanation for recent events? The delicate interplay involving father, mother, infant and physician is now complicated by the use of a vital organ of a baboon. One wonders how the animal was approached to give its informed consent.

As life gets more complicated for us Providers, I can only fall back on ancient wisdom: Attention all Health Care Providers.

Have short term goals as well as long ones. With love and enthusiasm, you can get through the next hour. If you made a mistake, learn from it and forget it; the next hour demands your undivided attention. You certainly can get through the next day, the next few days. You will make it through anatomy, son, or that last night on duty before your two day break, my daughter. PGY-1, you can survive this rotation.

Ask yourself, people, is there anything more interesting,

From 2609 N. Duke Street, Durham 27704.

more rewarding to you, than medicine? If there is, you had better be out and doing it soon. If not, dig in and enjoy the present. The past can't be undone; the future is uncertain, but for you, because you care, it can be a bright one. Hang tough, The Sage is watching you with love. He still cares too, after these many years in practice, and there is no bureaucracy, no third party that can take that away. Thanks Dr. Peabody, we still remember you.

EDITORIAL

Sometimes It's Tough to Make a Living

John H. Felts, M.D.

ONE of the difficulties in making a living is constant exposure to things at work which can cause a multitude of problems. The names of some of them — housemaid's knee, weaver's bottom — can't be improved upon nor can the ones given to some injuries incurred at leisure — jogger's nipple, tennis elbow. And tennis elbow can strike in the non-swinging arm of those who don't even play tennis, provoked by less athletic maneuvers.

In recent months, the textile industry has been criticized because many of its workers, male and female, develop arthritic difficulties in their wrists and shoulders, thoracic outlet and carpal tunnel syndromes, for example. The industry is accused of all sorts of nefarious deeds because it can't seem to produce a symptom-free, risk-free workplace and is, it sometimes seems, held responsible for its employees' pre-employment anatomical development. There are many textile manufacturers really genuinely concerned who are doing what they can to ease the strain, meanwhile wondering how to cope with imports from the Orient.

There aren't many easy solutions for either problem but the industrial worker may be better off in terms of work hazards and third-party medical coverage than the fast disappearing, much written about, oft idealized small farmer in the United States. Some of our politicians still sound on television, today's synthetic stump (or hustings if you prefer), as if more than 50% of us live in the country, acquire our moral stamina from the soil and can't survive without tobacco, milk or honey price supports from Washington, all the while demanding that government get off our backs. The small farmer, now commuting to town to work during the day at a factory, needs some attention at a practical level, not from remote reformers, because his family is subject to all natural risks imaginable. When there were more farmers, cotton and the boll weevil and tobacco and blue mold made headlines but now carcinogenesis and brown lung threaten. Little wonder farmers continue to go to town for work which isn't as demanding as that on the idyllic family farm reached by muddy roads, threatened by dry wells and blessed by cold privies which certainly contributed to making constipation a major medical problem only yesterday. Cold, even icy, wooden seats and bare bottoms are rarely compatible.

Yet when occupations are changed from country to town or even when we acquire new things, we enter new zones of risk as we escape from the old. Take the Honda hip, as yet unreported in our medical literature. A patient of mine, enticed by Japanese design and the promise of more economical maintenance, traded in his car for a new Honda Civic. His build, however, was such and its left front seat such that they didn't fit and he developed right hip pain and stiffness after driving short distances. Highly touted nonsteroidal anti-inflammatory drugs provided little relief. Cure of his Honda hip was economic but at some financial loss in trading his new Honda for a car his size.

Hands and wrists come in for trauma too. The farmer's wife who gets tobacco-seasonal carpal tunnel syndrome requiring surgery in the winter, for one. And what of the cotton buyer at his work for more than 30 years who was referred before we could measure parathyroid hormone in the blood, because erosions of the medial aspects of his second (middle) phalanges were interpreted radiologically as indicative of hyperparathyroidism? A cotton buyer tests for tensile strength and other characteristics by grasping a sample between the first and second fingers of each hand and pulling it apart. More than 30 years of sampling can cause traumatic erosions of bone. And, finally, the middle-aged lady with recent onset of hand pain and stiffness without a history suggestive of Raynaud's phenomenon or physical or laboratory signs indicative of arthritis. A careful occupational history told the tale. She was a chicken packinghouse worker who supervised a conveyor system transporting carcasses for a last washing before packing. She had been at the job for several years but a few weeks before her symptoms began, a new system, which fed water from above as well as below, had been installed. The water was cold, her hands stayed cold and wet and she had hand angina from vacoconstriction and ischemia induced by the cold. When she was transferred to a dry job, her symptoms disappeared.

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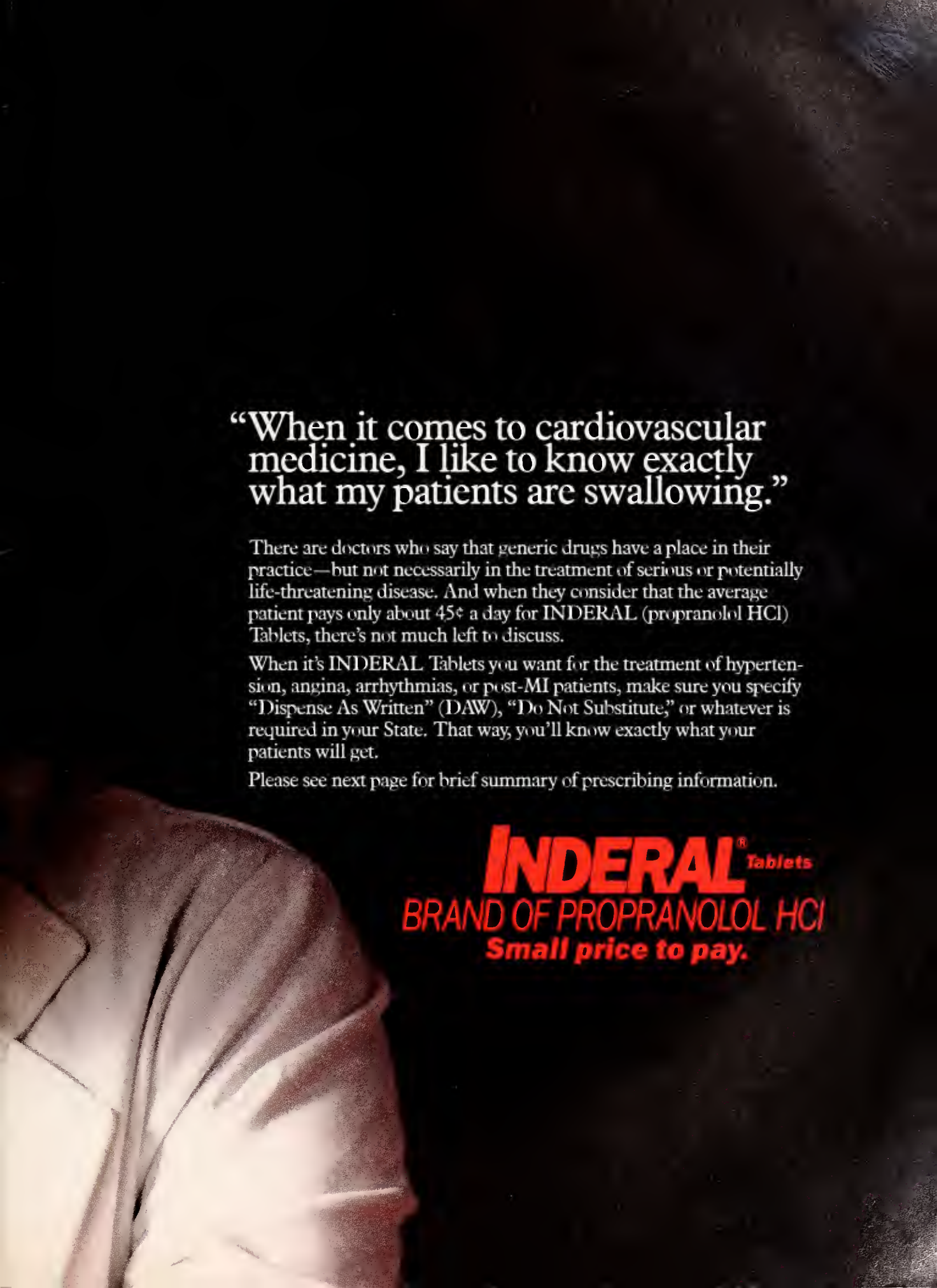
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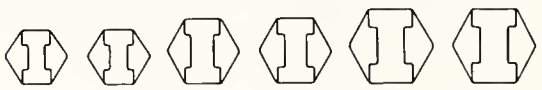



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WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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SPECIAL ARTICLE

Balloons on the CCU

Charles Shunior, B.S.N.

• *The dying of a vital, vibrant young woman on the CCU brings some changes to the high-tech approach the unit usually employed with its seriously ill patients.*

BALLOONS are a gesture of mirth, connoting youth and playfulness. But when a garland of balloons recently appeared in our coronary care unit, it commemorated not a birthday or a promotion but a death, and a painful, tragic one at that. Yet it occurred to no one to regard the gesture as ghoulish or in poor taste. The donor was a young university instructor whose wife had died exactly one year before in our Coronary Care Unit (CCU).

Before Elaine came to the CCU we rarely questioned our approach to gravely ill patients. The issue seemed basically straightforward: we saw death as the fundamental enemy and any time rescued from its clutches as a victory. The struggle admitted little ambiguity. We were heroes in a John Wayne western; our patients, helpless frontier maidens; death, a savage ravager. If we grudgingly conceded that, for certain patients, "the time had come," it was for some other area of the hospital to direct this inferior script. "No codes" were alien to the moral landscape of the CCU. As long as a patient remained in our province our directive seemed clear: wrest minutes or days from the maw of death.

We knew that outside the austere domain of intensive care units a different way of understanding death and dying had been gaining some prominence. Spurred to consciousness by the hospice movement and by writers such as Elisabeth Kubler-Ross, death was seen not merely as an endpoint but as a process which could be accomplished with greater or lesser skill, grace, and reward. One ramification of this perspective was a therapeutic stance oriented not toward an impossible recovery or the staving off of an inevitable death but toward helping the patient to die well.

To us in the CCU the urgings of thanatologists seemed a remote whisper. Reversible emergencies, not chronic terminal illness, were the grist for our mill. Nevertheless, troubling questions lingered behind the backdrop of our familiar routine. What of patients who suffered acute illnesses on top of irreversible disease processes, such as the metastatic cancer patient who has sustained a heart attack? We treated such patients with a split mind. We noted their presumably terminal condition, but allowed them to be swallowed into the high-tech gut of the hospital's "business-as-usual" therapy system.

From the Coronary Care Unit, North Carolina Memorial Hospital, Chapel Hill 27514.

Into the middle of our veiled ambiguity came Elaine, fighting for breath in severe congestive heart failure. A year ago she had been one of our telemetry patients, and we had known her with affection as an attractive young woman whose sense of fun was undampened by a diagnosis of viral cardiomyopathy. Relatively symptom-free during her previous hospitalization, she had kept the staff holding their breath and smiling despite their concern as she sailed down the corridors using her IV pole as a scooter. Her large brown eyes twinkled with vitality as she talked about issues of life and a death that seemed so distant.

She came back to the CCU after a rapid and drastic decompensation, already on a respirator and dependent on intravenous cardiotonic medicines. Within a short while sepsis and renal failure were added to the list of her problems. Elaine's room eventually looked like a high-tech health fair as her bed, already lost in a forest of infusion pumps, became surrounded by a cooling blanket generator, a cardiac output computer, and a panoply of peritoneal dialysis equipment. Somewhere in the middle of all these gadgets was a young woman, scared, hungry to live, whose heart was hopelessly broken. Although, by themselves, her acute emergencies or complications were potentially reversible, even her candidacy for heart transplantation had been ruined by her systemic complications.

With a patient as young and lively as Elaine, the nursing and medical staff are drawn to hope for miracles. We played all our aces, fighting day by day for the miracle to happen. And Elaine fought for it too. A partner in all medical decisions, she struggled to the end for more time, requesting only days before her death that a chest tube be inserted, buying her more hours or days at the cost of more suffering.

Even as we hoped for miracles, the massive reality of death was our ever-present backdrop. No one, from the attending physicians to Elaine herself, had any real illusions about the final outcome of the struggle. During one of Elaine's relatively uncomplicated periods I permitted myself to think that her disease was in remission and that she might yet recover sufficiently to leave the CCU. When I shared this idea with Elaine she smiled and shook her head as a mother might to disillusion a child's over-enthusiastic assessment of the power of Santa Claus.

But if Elaine were not a "viable" patient, what was the point of all our efforts and all her pain? If our Faustian struggle against death were doomed to fail, should we not

in that case withdraw her elaborate life supports and let her go in peace? Elaine herself resolved this ethical dilemma by her unrelenting thirst for life, for one more day of struggle. The high-tech gadgetry kept beeping; and the dialysate, the antibiotics, and the cardiotonic drugs kept flowing.

Gradually we sketched in the outlines of a new way to care for terminal patients in an intensive care unit setting. This model affirmed the propriety of advanced medical support for terminal patients such as Elaine. The tradeoffs between comfort and safety were not automatically made in favor of comfort. Swan-Ganz catheters, chest tubes, and dialysis machines were seen to be appropriate aspects of dying, as they were for Elaine. But in the context of all this high-tech life support we endeavored to provide low-tech life enhancement, remembering that death is always in the background of the scenes we enact in the CCU. Elaine helped us learn to focus day by day not on "saving" patients at all costs nor on helping them directly to "prepare for death," but rather on creating a space for the patient in which maximum real living could continue. In answer to the question "Why are we expending so much time, so many resources, and so much emotion to help a dying girl live a few more days?" we could answer that, from the perspective of eternity, all of us have only a few days left and that the goal of the healing arts should not be merely to stave off death but to empower us within those few days to approach the highest possible personal attainment. In order for this answer to be honest we must focus — even in the CCU — not merely on the protection of life but on its enhancement.

So it was that housestaff and nurses found themselves gathered around Elaine's bed serenading her with her favorite folksongs while the medical resident joined her husband in a guitar duet. And so it was that nurses and the respiratory department solved the complicated problems of transporting an intubated patient from the CCU to an outdoor patio in order to reunite Elaine with her somewhat bewildered but faithful dog. And that members of Elaine's family were present at her bedside around the clock; sometimes merely being with her; sometimes browsing through old photo albums, affirming the goodness, the fullness of her life. During those times when Elaine was not intubated, her mother would share with her the hardest words, making funeral plans and talking about life after death.

A member of the Department of Psychiatry who had known Elaine before her hospitalization came frequently to the CCU during the last weeks in order to coach her in meditation techniques for stress reduction.

A journal was kept at Elaine's bedside, and visitors to her room, whether staff or family, were encouraged to write their observations, reflections, and suggestions. We originally thought that the book would improve professional communication among the many persons who shared Elaine's care, but it soon became evident that writing in the journal provided the staff with a record of our own growth as nurses, doctors, and human beings.

One morning Elaine's heart rate began to slow down and its rhythm deteriorated. I whispered to her that the time was drawing near, that I knew she was ready. Using a theme we had explored for meditation purposes, I reminded her that if she softened herself, gave up resistance, the wave would take her gently, as a mother carries a child to bed. She closed her eyes, took her husband's hand, and died.

The memorial service held the next week for Elaine employed the Quaker format of allowing persons to spontaneously "witness" their love and grief. Physicians, nurses, technicians, personal friends and family all spoke. Passages from the bedside journal were read and we all joined in singing songs she had loved. Besides being a memorial to Elaine, this service commemorated acceptance by the hospital community of our new way of caring for dying patients in ICUs. Near the heart of our grief was the satisfying knowledge that our unit had found an identity as a healing environment for the terminally ill ICU patient.

In the months following Elaine's death we have tried to strengthen this healing environment. The unit has been redecorated to look less forbidding, more homelike. Noise control is emphasized, and visitation policies are custom-tailored to the emotional and physical needs of the patients. Staff are routinely oriented to techniques of stress reduction and emotional counseling. Periodic group discussions on issues of death and dying help us to clarify our own responses to guiding patients through the valley of the shadow.

Above all Elaine, and the balloons that came in her memory, remind us to bring to our patients songs as well as medicines. Life — with its fantastic range of physical and emotional cravings, its need not just for bread, but for roses — is as miraculous in its last hours as its first.

SCIENTIFIC ARTICLE

When Crohn's Disease Is Not Crohn's Disease

David A. Forsberg, Thomas C. Wall, M.D., John T. Garbutt, Jr., M.D.

• *The key to Crohn's disease is chronicity.*

THE diagnosis of inflammatory bowel disease carries serious long-term implications. Both Crohn's disease (regional enteritis) and non-specific ulcerative colitis are considered illnesses with poor prognoses. When the physician makes this diagnosis he must understand that he is possibly committing the patient to (1) long-term medication, (2) decreased insurability (health and life insurance are difficult to obtain and more costly), (3) difficulty in securing employment and (4) severe psychosocial stress as the patient becomes familiar with the expected course of his disease.

The following case report illustrates the danger of premature diagnosis.

Case Report

A previously healthy 22-year-old white male medical student presented to the Emergency Room with a history of abdominal pain, malaise, lightheadedness and low grade fever of 48 hours' duration. He denied nausea, vomiting, or change in bowel habit. On physical exam vital signs were normal, temperature was 37°C and right lower quadrant pain maximal at McBurney's point with mild rebound tenderness was present. Rectal exam was normal except for a tender right gutter, and stool was guaiac negative. Pertinent lab values included WBC 8100 with a normal differential. A flat plate of the abdomen revealed possible calcification in the right lower quadrant consistent with an appendolith.

A tentative diagnosis of appendicitis was made and the patient underwent surgical exploration. Operative findings included a normal appendix and an 8 cm length of thickened, inflamed terminal ileum. Intraoperative cultures for routine pathogens were negative. A diagnosis of terminal ileitis, probably Crohn's disease, was made. Simple appendectomy was performed without bowel resection. The patient was started on a prednisone taper and later sulfasalazine (Azulfidine) therapy. The patient and his family were informed of the existing diagnosis of regional enteritis. It was recalled that a distant cousin had Crohn's disease.

Since the patient was a medical student he had some knowledge of inflammatory bowel disease and its sequelae. His further reading on the subject was clearly depressing. Further emotional stress ensued when he was informed that he might have to consider changing his career goals in surgery as a result of the unpredictable and serious implications of this illness.

From the Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham 27710.

However, the postoperative course was complicated by the onset of profuse bloody diarrhea on the fourth day. There was no history of foreign travel, seafood ingestion, animal exposure, antibiotic exposure, or homosexual experience. Proctoscopy at that time revealed diffuse friable granularity, no discrete ulcers and a purulent stool on microscopic smear. Cultures for enteric pathogens were positive for Campylobacter fetus jejuni. Although subsequent x-ray revealed changes felt to be typical of Crohn's disease in the ileum and cecum (figure 1, left), the clinical diagnosis was now felt to be bacterial dysentery due to Campylobacter.[1-5] Prednisone and sulfasalazine were discontinued and the patient was treated with a 7 day course of erythromycin 500 mg po q.i.d. with complete resolution of all symptoms. He has remained well for an 18-month follow up and repeat UGI with ileal x-ray is now normal (figure 1, right).

Table 1
Differential Diagnosis of Dysentery

Specific Infections
Campylobacter
Shigella
Salmonella
Yersinia
Gonorrhea
Tuberculosis
Lymphogranuloma venereum
Non-LGU Chlamydia
Amebiasis
Schistosomiasis
Syphilis
Fungal infections (e.g., Histoplasmosis)
Vibrio enterocolytica
Viral etiologies
Pseudomembranous colitis
Non-Specific Inflammatory Bowel Disease
Ulcerative colitis
Crohn's disease
Mechanical Factors
Radiation colitis
Chemical proctitis
Ischemic colitis
Systemic Diseases
Amyloidosis
Systemic lupus erythematosus
Hemolytic-uremic syndrome
Scleroderma
Vasculitis
Behcet's syndrome
Neoplasia (lymphoma, leukemia)

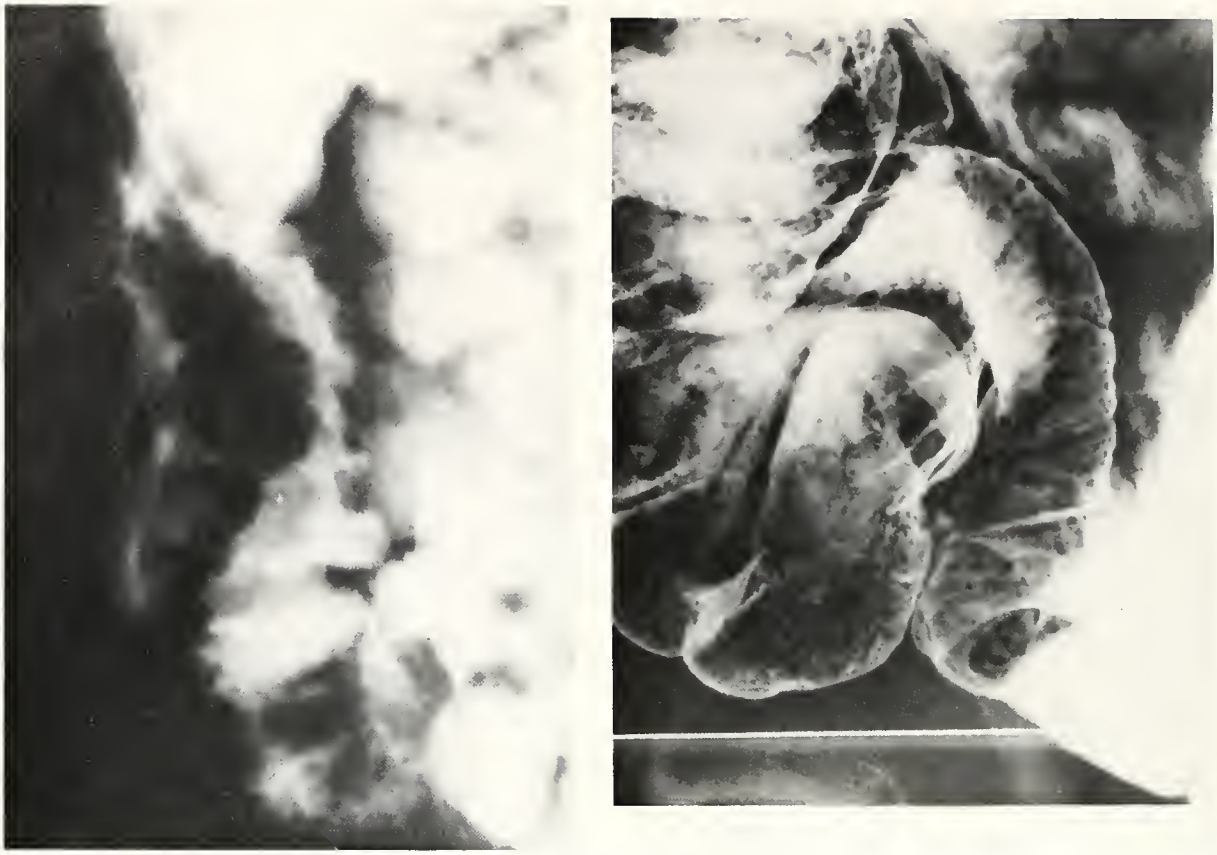


Figure 1. *Left: Severe inflammation of distal ileum and cecum. Right: Complete resolution of inflammation after antibiotic treatment.*

This case illustrates that a diagnosis of regional enteritis or ulcerative colitis generally should not be made at the time of first symptoms. Rather the diagnosis of inflammatory bowel disease (ulcerative colitis, regional enteritis) should imply chronicity and recurrences and is a diagnosis of exclusion. Many infectious etiologies may produce ileitis or colitis mimicking inflammatory bowel disease.[6, 7] These include Campylobacter, Shigella, Salmonella, and Gonococcal infection in the U.S., as well as amoeba and tuberculosis if foreign travel has occurred. Appropriate cultures are the key to correct diagnosis. While uncommon, such an acute infection may mimic a surgical abdomen, necessitating laparotomy.[8, 9] At such a time, appropriate cultures should be obtained. Mechanical factors such as radiation or ischemia must also be considered but the history is usually self-evident. Pseudomembranous colitis due to prior antibiotics usually has a classic endoscopic appearance. A variety of systemic illnesses may also have gastrointestinal manifestations and must be included in the differential diagnosis. Table 1 presents a partial list of the diseases which should always be considered before making the diagnosis of inflammatory bowel disease.

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SCIENTIFIC ARTICLE

Familial Thrombotic Disorders

John J. Stuart, Ph.D., M.D. and M. Robert Cooper, M.D.

• *Two brothers with recurrent thrombosis and phlebitis in their legs have low levels of protein S, a recently discovered natural anticoagulant.*

IN the past thirty years our knowledge of the blood clotting system has advanced from crude experiments employing nothing more complicated than test tubes to complex enzymology yielding almost overwhelming detail about molecular structure and kinetics. These advances have greatly improved the diagnosis and treatment of bleeding disorders so that it is now rare to find one the cause of which is undiagnosable. Such is not the case, unfortunately, with thrombotic disorders. Despite a wealth of information about the natural anticoagulants existing in the plasma and endothelial cells, the cause of venous thrombosis in many patients remains obscure and the treatment non-specific.

Recently the discovery of two new naturally occurring anticoagulants, proteins C and S, has explained the cause of two rare familial thrombotic tendencies.[1, 2] This report describes the clinical course of protein S deficiency in two brothers and will attempt to review in a practical fashion the subject of familial thrombotic disorders.

Case Report

The patient first developed deep venous thrombosis of the right leg at age fourteen after a fall. Despite treatment with warfarin, deep venous thrombosis recurred requiring hospitalization for treatment with heparin. At age sixteen, he developed a severe rash from warfarin and was changed to subcutaneous heparin on an outpatient basis. Laboratory evaluation at this time revealed the following tests to be normal: prothrombin time, partial thromboplastin time, thrombin clotting time, fibrinogen electrophoresis and antithrombin three level by immunologic assay. Heparin therapy did not prevent recurrent lower extremity thrombophlebitis which was, however, controlled when he was placed on the long-acting vitamin K antagonist Diphenadione. Control of his disease continued for six years punctuated by recurrent episodes of hemorrhage due to excessively prolonged prothrombin times. This problem prompted discontinuance of his anticoagulation at age 23 but recurrent deep venous thrombosis followed within a month. Diphenadione was restarted but was stopped six months later because the drug was withdrawn from the market. Since that time his phlebitic tendency has been reasonably well controlled by 10,000 units of heparin self-administered twice daily, but superficial thrombophlebitis of the legs, abdomen and chest occurs sporadically. Post-phlebitic syndrome with recurrent malleolar stasis ulcers has been a major source of disability.

The propositus has three siblings. A younger brother developed recurrent lower extremity phlebitis at age fifteen, also after mild trauma, and has been on warfarin since that time. A sister and another younger brother have no symptoms, nor do the parents. The only other family member with phlebitis is the paternal grandmother who developed it at age 58 after undergoing hip surgery. Table 1 shows the protein S levels in this family as determined by Dr. Philip Comp.[3] Presumably, the brothers are homozygous for protein S deficiency while their asymptomatic parents are heterozygotes. The phlebitis in the grandmother with a normal protein S level can be related to antecedent surgery.

Protein C and Protein S Deficiency

Deficiencies of protein C and protein S are similar clinically, presenting as recurrent deep and superficial venous thrombosis. These two naturally occurring anticoagulants are similar also in being dependent on vitamin K for their synthesis as are the procoagulant clotting factors II, VII, IX, X. The activation of protein C probably occurs simultaneously with the laying down of fibrin clot at an injury since protein C, like fibrinogen, is activated by thrombin.[4] In the case of protein C, the thrombin must be bound to a protein, thrombomodulin, which in turn is bound to endothelial cells, in order that activation take place. Activated protein C is capable of destroying activated factors V and VIII proteolytically and therefore damping clot formation. The thrombomodulin-protein C pathway exerts, therefore, negative feedback inhibition on clot formation.

Protein S appears to function as a cofactor for activated

Table 1

Individual	Age	Symptomatic	Protein S Level (%)
Propositus	29	Yes	<5
Brother	18	Yes	<5
Brother	16	No	80
Sister	25	No	85
Father	48	No	15
Mother	47	No	30
Paternal grandmother	73	Yes	101

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Table 2
Familial Thrombotic Disorders

Disorder	Diagnostic Test	Availability of Test
Antithrombin III deficiency	Immunologic and functional assay	Widely available
Protein C deficiency	Immunologic and functional assay	Research lab only
Protein S deficiency	Immunologic and functional assay	Research lab only
Plasminogen deficiency	Immunologic and functional assay	Some commercial labs
Plasminogen activation deficiency	Functional assay	Research lab only
Fibrinolytic inhibitors	Functional assay	Research lab only
Dysfibrinogenemia	Thrombin clotting time	Widely available
	Kinetic analysis	Research lab only

protein C.[5] By binding to protein C, it greatly increases the rate at which activated protein C is able to destroy activated factor V.

The Naturally Occurring Anticoagulant System

Prior to the discovery of protein C and protein S, the naturally occurring anticoagulants in the fibrin-forming system (the interacting platelet system will not be discussed) were limited to plasminogen and antithrombin III (heparin cofactor). In addition, some molecular variants of the fibrinogen molecule were known to result in a thrombotic tendency. Each of these proteins will be briefly discussed.

Plasminogen

The concentration of plasminogen in human plasma is about 21 mg/100 cc. During tissue injury plasminogen, activated by enzymes released from the injured endothelium, becomes the active serum protease plasmin. Because plasminogen has a high binding affinity for fibrin clot, under physiologic conditions plasmin is generated in proximity to the protein (fibrin polymer) that it is meant to destroy. Any plasmin generated in the blood stream in the vicinity of the clot is neutralized by inhibitor proteins of which the most important is the alpha-2-plasmin inhibitor. Thereby non-specific action of plasmin on circulating fibrinogen and coagulation factors such as V and VIII is prevented. In the pathologic state of disseminated intravascular coagulation, so much plasmin is generated that the inhibitor system is overcome and large amounts of fibrin(ogen) degradation products are generated.

As might be expected, mutation resulting in amino acid substitutions in plasminogen can result in a less active enzyme and an inherited tendency to deep venous thrombosis. In the cases reported so far, the immunologically measurable plasminogen has been normal but the mutant enzyme has had decreased functional activity.[6, 7] Deficiencies of endothelial plasminogen activation[8] and naturally occurring inhibitors of fibrinolysis[9] have also been reported to result in thrombotic disease.

Antithrombin III Deficiency

The plasma protein antithrombin III (AT-III) is the most important inhibitor of thrombin. A partial deficiency of AT-III causes recurrent deep venous thrombosis. The homozygous condition with zero AT-III levels has not been observed and is probably incompatible with life. The anticoagulant action of heparin is mediated through AT-III. The non-covalent AT-III-heparin complex has a greatly increased affinity for thrombin and other activated procoagulant factors when compared with AT-III alone. The prevalence of AT-III deficiency has been estimated at one per 2000.[10] The inheritance pattern is autosomal dominant with variable penetrance. Usually the antigenic level of AT-III is decreased but occasional families have a pattern of functionally deficient AT-III which is present in normal quantities when measured with standard immunologic techniques.[11]

Dysfibrinogenemia

The process by which the soluble plasma protein fibrinogen becomes a stabilized fibrin clot through the action of thrombin and factor XIII is complex and leaves much room for errors of nature. More than seventy molecular variants of the fibrinogen molecule have been discovered, most of which are inherited in an autosomal dominant fashion and result either in a bleeding or in a clotting diathesis,[12] but may be asymptomatic. Paradoxically, in some families both bleeding and clotting tendencies coexist. Occasionally the thrombotic tendency affects arteries as well as veins. The concentration of fibrinogen measured by standard immunologic or clotting methods is usually normal. The abnormality is generally easily recognizable, however, because it almost always results in a prolonged thrombin clotting time (TCT). Confirmation of the diagnosis would result from ruling out any other cause of a prolonged TCT or better, from kinetic studies of fibrin monomer formation, polymerization and crosslinking. Treatment of the disorder by anticoagulants is usually successful.

Summary

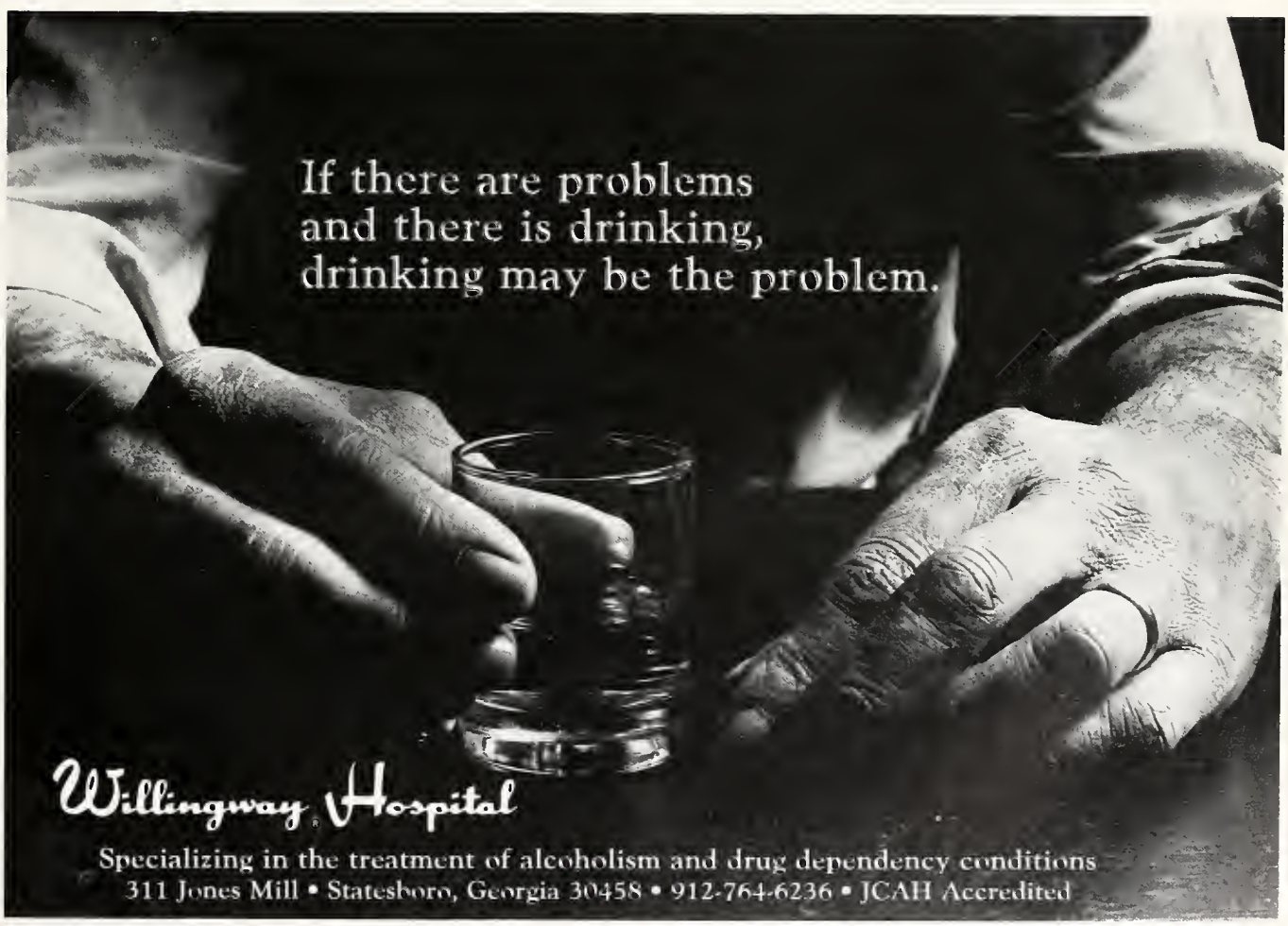
Opportunities are vast for the occurrence of mutations adversely affecting the function of the many components of the naturally occurring anticoagulant system. A family history of recurrent thrombophlebitis and thrombophlebitis difficult to control with warfarin and heparin are clues that a familial disorder may be present. The lack of other affected family members does not rule out the diagnosis, however, since one may be dealing with a new mutation or with variable penetrance of the disorder. Generally, life-long anticoagulation with warfarin is the treatment of choice.

Table 2 shows the most common familial thrombotic diseases and the diagnostic tests available. There is no doubt that presently unclassifiable disorders exist, the cause of which will eventually become clear as our understanding of hemostasis increases.

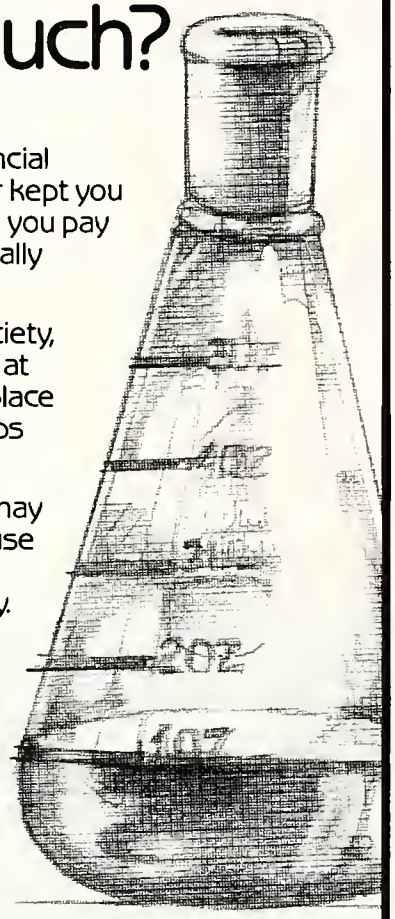
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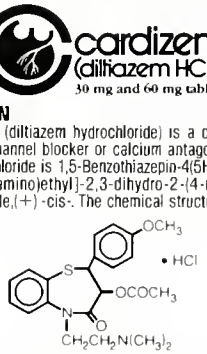
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CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm. CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.
asthenia (1.2%), AV block (1.1%). In addition, the following ev
were reported infrequently (less than 1%) with the order of pres
tion corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, brad dia, palpitations, congestive heart fai syncope.
Nervous System:	Paresthesia, nervousness, somnole tremor, insomnia, hallucinations, and amn
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vom mild elevations of alkaline phosphatase, S SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensi
Other:	Polyuria, nocturia

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episode vasospastic angina developed periods of transient asymptor asystole approximately five hours after receiving a single 6 dose of CARDIZEM.

The following postmarketing events have been reported quently in patients receiving CARDIZEM: erythema multiforme kopenia; and extreme elevations of alkaline phosphatase, S SGPT, LDH, and CPK. However, a definitive cause and effect bet these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been lim Single oral doses of 300 mg of CARDIZEM have been well tole by healthy volunteers. In the event of overdosage or exagge response, appropriate supportive measures should be employ addition to gastric lavage. The following measures may be consid

Bradycardia	Administer atropine (0.60 to 1.0 mg). If is no response to vagal blockade, admin isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed degree AV block should be treated with diac pacing.
Cardiac Failure	Administer inotropic agents (isoproter dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarte bitartrate).

Actual treatment and dosage should depend on the severity c clinical situation and the judgment and experience of the tre physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 m and from 560 to 810 mg/kg, respectively. The intravenous LD_{5} these species were 60 and 38 mg/kg, respectively. The oral LL dogs is considered to be in excess of 50 mg/kg, while lethality seen in monkeys at 360 mg/kg. The toxic dose in man is not kn but blood levels in excess of 800 ng/ml have not been assoc with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic C nary Artery Disease or Angina Pectoris at Rest Due to C nary Artery Spasm. Dosage must be adjusted to each pati needs. Starting with 30 mg four times daily, before meals ar bedtime, dosage should be increased gradually (given in div doses three or four times daily) at one- to two-day intervals optimum response is obtained. Although individual patients respond to any dosage level, the average optimum dosage r appears to be 180 to 240 mg/day. There are no available data con ing dosage requirements in patients with impaired renal or he function. If the drug must be used in such patients, titration shou carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort a anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be s coadministered with short- and long-acting nitrates, but t have been no controlled studies to evaluate the antian effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (0088-1771-47) and in Unit Dose Identification Paks of 100 (0088-1771-49). Each green tablet is engraved with MARION on side and 1771 engraved on the other. CARDIZEM 60-mg sc tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Dose Identification Paks of 100 (NDC 0088-1772-49). Each ye tablet is engraved with MARION on one side and 1772 on the o

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SCIENTIFIC ARTICLE

Screening for Congenital Hypothyroidism in North Carolina — 1979-1984

Robert P. Schwartz, M.D.

- *The cost of diagnosing one case of congenital hypothyroidism in North Carolina is $9,618. The cost of institutionalizing one person for 30 years in North Carolina is $1,215,450. The savings afforded by screening are obvious.*

CONGENITAL hypothyroidism is associated with a high incidence of mental retardation. Before screening programs, congenital hypothyroidism accounted for 1-2% of admissions to institutions for the mentally retarded. Only 10% of infants with this disorder attained an IQ of greater than 90 if treatment was delayed over 6 months. The cause of delayed diagnosis is the nonspecificity of signs and symptoms of congenital hypothyroidism which include prolonged gestational age, large posterior fontanel, constipation, jaundice, feeding problems, umbilical hernia, hypothermia, lethargy, and hypotonia. An enlarged tongue is often not present in the newborn period.[1]

In 1972, Klein et al reported that 78% of infants whose congenital hypothyroidism was treated before 3 months of age had an IQ of greater than 85.[2] In 1973, pilot programs for hypothyroid screening were started in Quebec and Pittsburgh. Between 1976-1981, 717,123 infants were screened for hypothyroidism in Massachusetts. One hundred forty-six infants were detected with congenital hypothyroidism for an incidence of 1:4600 live births. Ninety-five of these infants had thyroid scans. Forty-three percent had ectopic thyroid tissue, 22% goitrous hypothyroidism, and 35% had hypoplastic or aplastic glands. In only 4% of these infants was the diagnosis suspected clinically.[3]

In January 1979, a program for hypothyroid screening began in North Carolina. Through the efforts of the Department of Human Resources, the North Carolina Pediatric Society, and the leadership of Representative Patricia Hunt and Senator Ollie Harris, a bill (House Bill 372) to provide funding for hypothyroid screening was passed in the North Carolina legislature. The bill provided $120,000 a year to establish a statewide newborn screening program for congenital hypothyroidism. Between 1979-1982, screening tests were performed by the state laboratory in Raleigh and Dr. George Summer's laboratory in Chapel Hill. Since 1982, almost all tests have been performed by the state laboratory.

Protocol for Thyroid Screening

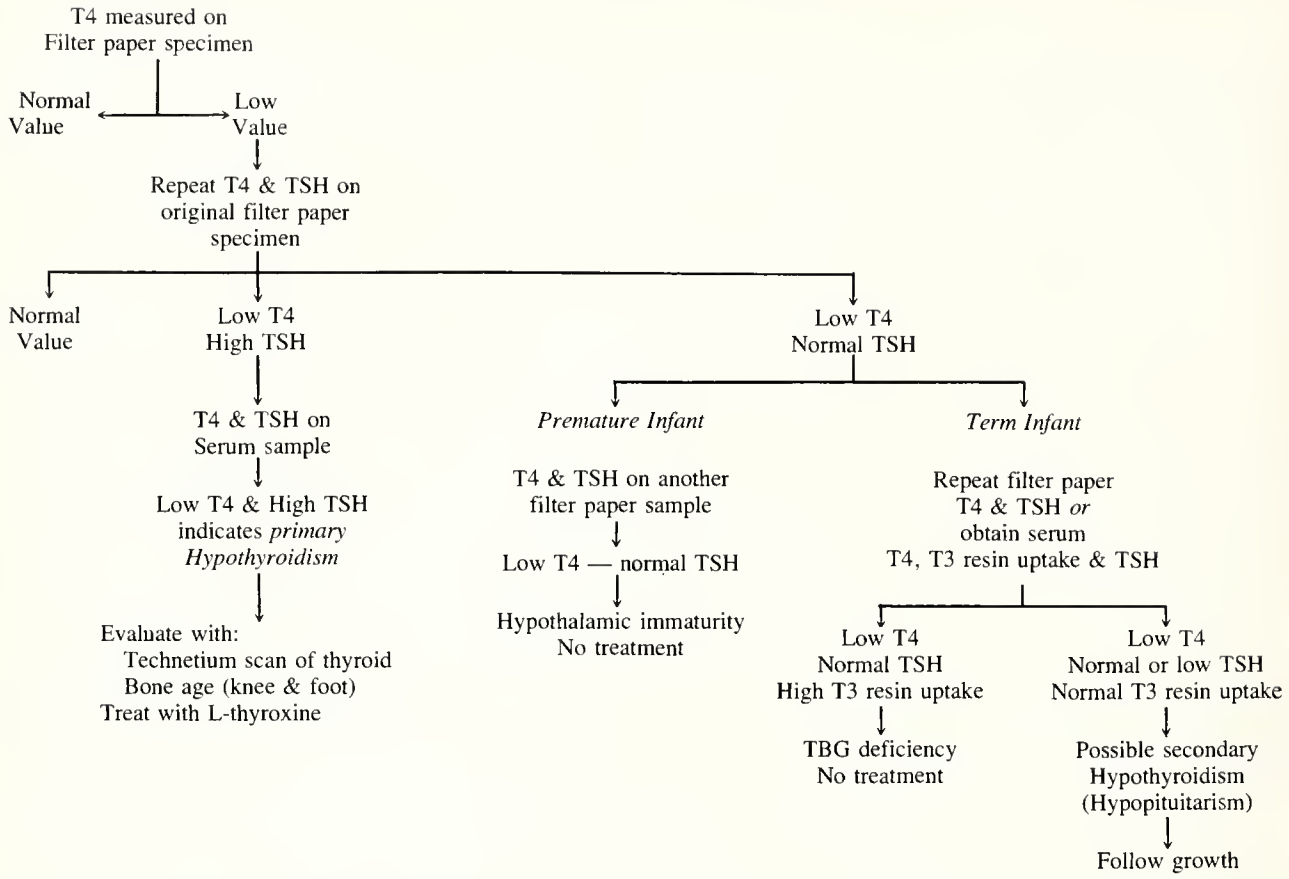
Blood samples for screening for hypothyroidism and phenylketonuria are obtained by heelstick on all infants prior to discharge from the nursery, regardless of age or feeding status. Infants discharged before 24 hours of age should have the tests repeated by 2 weeks of age. Premature or ill infants, or infants on parenteral feedings should have the tests performed by 7 days of age.

The protocol for hypothyroid screening is to first obtain a filter paper T4 (figure 1). If the T4 is low, an additional T4 and a TSH are performed on the same filter paper specimen. If the repeat filter paper T4 is low with an elevated TSH, the physician is notified by the state laboratory and a STAT serum T4, T3 resin uptake, and TSH are obtained. Infants with a low serum T4 and elevated TSH should have a bone age x-ray (PA of the knee and oblique of the foot) and a technetium thyroid scan. The bone age x-ray may indicate the degree of prenatal insult to skeletal maturation. Most term infants will have distal femoral, proximal tibial and cuboid epiphyses present at birth. The thyroid scan is done for genetic counseling. Infants with a normal sized or enlarged gland on thyroid scan may have a defect in the synthesis of thyroxine. This can be a familial disorder with autosomal recessive inheritance. Absent, ectopic, or dysgenetic thyroid glands can also be identified by thyroid scanning. These are usually not inherited disorders.

Many infants are observed to have a low filter paper T4 and normal TSH. Causes of this condition include prematurity, a deficiency of thyroid-binding globulin (TBG), hypopituitarism, and the so-called euthyroid sick syndrome. When the combination of low T4 and normal TSH is observed, a repeat filter paper T4 and TSH should be obtained. In premature infants, if the repeat T4 is low and the TSH is again normal, it is not necessary to perform any further studies since the low values are due to a delay in maturation of the hypothalamic-pituitary-thyroid axis. In a term infant with a low T4 and normal TSH, serum may be obtained for a T4, T3 resin uptake (an indirect measure of TBG binding sites not occupied by thyroxine), and TSH. A low T4 with an elevated T3 resin uptake is diagnostic of TBG deficiency. A direct measurement of TBG by radioimmunoassay will confirm the diagnosis. Infants with TBG deficiency are euthyroid and require no treatment. Hypopituitarism can also be associated with a low T4 and a normal or low TSH. Extensive evaluation for hypopituita-

From the Department of Pediatrics, Charlotte Memorial Hospital & Medical Center, Charlotte 28232.

Figure 1. *Protocol for Hypothyroid Screening*



rism is not indicated unless there are other symptoms or signs such as hypoglycemia or poor growth. The hypothyroidism which sometimes accompanies hypopituitarism has not been observed to cause mental retardation.

Infants with congenital hypothyroidism are started on treatment with Levothyroxine at a dose of 10 μg/kg/day (0.025-0.05 mg). Thyroid function tests are repeated in 2-4 weeks and are then done every 3 months for the first year and every 4 months the second year. The treatment goal is to keep the serum T4 in the mid to upper range of normal for the age of the infant (8-12 μg/dl). It may take several months for the TSH to fall into the normal range.[4] Linear growth is also an excellent parameter of adequacy of thyroid hormone replacement, and should be followed closely.

Thyroid Screening in North Carolina

Between January 1979 and April 1984, 408,259 North Carolina infants were screened for hypothyroidism. Fifty-eight infants were found to have congenital hypothyroidism, an incidence of 1:7039 (table 1). The decreased incidence of congenital hypothyroidism in North Carolina compared with Massachusetts (1:4600) is related to racial population differences. In Massachusetts, 6-7% of infants are black. Thirty-one percent of North Carolina births in 1983 were black. Only two of the 58 North Carolina cases of congenital hypothyroidism occurred in black infants. In Georgia, the incidence of congenital hypothyroidism is 1:7700. Thirty-seven percent of births in Georgia are black. The incidence of congenital hypothyroidism in Georgia was 1:5526 white infants, and 1:32,377 in blacks.[5]

Fifteen of the North Carolina cases have been seen in Charlotte (table 2). Eight were female and seven male. Fourteen of these infants had technetium thyroid scans; six were found to be athyrotic, five had lingual or sublingual glands, and three had goitrous hypothyroidism. Thyroid scan data are not available for the other North Carolina cases. The average age of treatment for the Charlotte cases was 29.8 days and for all North Carolina cases was 31.7 days (8-231 days). Besides the one infant with a delayed diagnosis at 231 days, another was detected at 82 days and nine at 45-70 days. All other infants were treated at less than 35 days of age. One case was missed by a technician recording error, but was fortunately diagnosed by a physician at 6 weeks of age. Another infant with a goiter was detected at 4 days of age before the screening test result was

Table 1
Thyroid Screening — North Carolina 1/79-4/84

Number screened	408,259	
Normal	395,124	(96.8%)
Insufficient sample	9,272	(2.3%)
Borderline value (41% premature infants)	13,077	(3.2%)
Primary hypothyroidism	58	(1:7039)

Table 2
Charlotte Cases of Congenital Hypothyroidism Detected by Screening Program

Patient	Birth weight (grams)	Sex	Age of treatment (days)	Thyroid scan	T4* µg/dl	TSH† µU/ml	Bone age
1	3773	F	16	Athyrotic	<1.0	>200	Delayed
2	2841	M	17	Athyrotic	1.7	230	Delayed
3	3295	M	47	—	7.4	65	—
4	4204	F	45	Goitrous	4.4	>100	—
5	4318	F	29	Lingual	7.5	59	Normal
6	3909	M	82	Goitrous	8.0	70	Normal
7	4318	F	11	Sublingual	<1.0	560	Delayed
8	3580	M	28	Sublingual	8.2	87	Delayed
9	3382	F	22	Lingual	6.3	279	Normal
10	3773	M	15	Lingual	7.0	>400	Delayed
11	3545	F	21	Athyrotic	<1.0	490	Delayed
12‡	2941	M	4	Goitrous	3.7	>500	Normal
13	3295	F	31	Athyrotic	<1.0	>60	Delayed
14	3664	F	26	Athyrotic	2.5	170	Delayed
15	4290	M	27	Athyrotic	2.3	>100	—

* Normal T4 for first week — 8-24 µg/dl, 1-12 months — 6-15 µg/dl.
† Normal TSH for first week — <20 µU/ml; normal TSH>one week — <10 µU/ml, borderline — 20-60 µU/ml, hypothyroid — >60 µU/ml.
‡ Detected by physician before screening result available.

available. Causes of delay in treatment included insufficient specimens, incorrectly filled out forms, a delay in mailing specimens to the state laboratory, administrative laboratory problems including a shortage of personnel, and delays in getting repeat specimens or a serum specimen.

Cost Effectiveness of Thyroid Screening

Hypothyroid screening has been shown to be cost effective. The cost to diagnose one case of congenital hypothyroidism in North Carolina is $9,618. The cost of institutionalization for 1 year in North Carolina is $40,515. If only 40% of the 58 cases in North Carolina had required institutionalization for 30 years (58 × 0.4 × $40,515 × 30 years), the benefit cost ratio would be 50:1. This ratio would be more impressive were the lost income of untreated or late treated patients taken into account.

Developmental Follow-up

Data on the development of North Carolina infants treated for congenital hypothyroidism are not available. In the New England screening program, however, 146 infants with hypothyroidism had IQs at 3-5 years of age that were similar to controls (siblings or patients with TBG deficiency). These infants were treated at a mean age of 24 days. Patients who had thyroid tissue on scan had higher T4 and lower TSH levels, and less retarded bone age than athyrotic patients. However, there was no difference in IQ in the two groups. The only factor affecting IQ was the adequacy of treatment.[3]

Funding is not yet available for developmental testing of hypothyroid infants detected by screening in North Carolina. It is hoped that an appropriation for this will be forthcoming, so that results in North Carolina can be compared with other programs.

Acknowledgment

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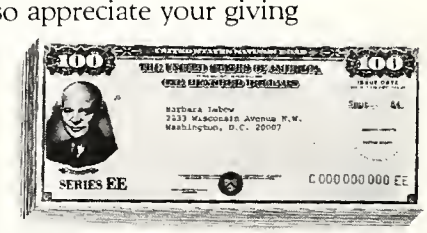


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SCIENTIFIC ARTICLE

Coccydynia: A Tail of Woe

Linda M. Frazier, M.D.

• *What should the doctor suspect in patients with a painful tailbone?*

PAIN in the coccyx is a common symptom, known as coccydynia or "coccygodynia" since 1859 when Simpson, the famous Edinburgh obstetrician, coined the term. From Simpson's specialty one can correctly guess that the condition is more common in women than in men. The following cases illustrate the spectrum of cause, course and treatment of this condition.

Case 1

Four years ago a 39-year-old woman fell, hitting her coccyx on the edge of a landscaping beam. The severe pain subsided after several weeks but intermittent pain, exacerbated by sitting or prolonged standing, remained. She had a habit of sitting with her feet propped on a stool because she was short statured. She had a history of poorly defined anxiety and depression. Two years ago she presented with an exacerbation of coccygeal pain. There was marked tenderness on palpation of the coccyx; pelvic and rectal examinations were normal. Coccyx x-rays showed no fracture (figure 1) and a sonogram of her pelvis showed no mass. A diagnosis of coccydynia was made. She was advised to sit on a doughnut pillow and to use a shorter chair; during two years of follow-up the symptoms have waxed and waned, but no serious coccyx pathology has developed.

Comment: Coccydynia occurs almost exclusively in women: in Hodge's series, 51 of 55 patients were women. Duncan found that 97% of 262 patients with coccydynia were women.[1, 2] The female preponderance is due to the anatomy of the female pelvis. The sacrum and coccyx are located much more posteriorly and the ischial tuberosities are farther apart in women than in men (figures 1 and 2) because the pelvis must accommodate a baby's head during birth. Both of these anatomic factors leave a woman's coccyx exposed and susceptible to trauma. Acute trauma, such as the fall in the sitting position which this patient sustained, is the most common etiology of coccydynia. Birth trauma is another common cause of acute coccydynia; some patients even fracture the coccyx during a difficult delivery. Our patient had an acute coccyx injury as well as repeated minor trauma to the coccyx when sitting with her feet propped up, which shifts her weight from her ischial tuberosities and thighs to her coccyx.

Our patient's history of anxiety and depression is worth noting. Some clinicians have found a preponderance of patients with psychologic problems among those with coccydynia. Wein[3] concluded that coccygeal pain may be part of a chronic pain syndrome caused by hysterical neurosis, although others disagree.[2]

Diagnostic evaluation begins after obtaining a suggestive history and includes a thorough physical examination. The coccyx should be tender to palpation. Rectal and pelvic exams are necessary to exclude rare causes of coccygeal pain such as pelvic infection or tumor. A pelvic ultrasound can help exclude a pelvic mass but is not always necessary. Close follow-up demonstrating a benign course confirms the diagnosis.

Treatment in the acute phase consists of hot sitz baths and nonsteroidal anti-inflammatory drugs. Thereafter, therapy is directed toward protecting the coccyx from further trauma by having the patient sit erect on a doughnut or



Figure 1. *Lateral coccyx x-ray of Case 1, a 39-year-old woman with coccydynia. Arrows indicate the posterior, exposed position of the coccyx normally seen in women.*

From the Division of General Medicine, Duke University Medical Center, Durham 27710.



Figure 2. *Lateral coccyx x-ray of 36-year-old man without coccydynia. Arrows indicate the more protected anterior position of the coccyx normally seen in men.*

U-shaped pillow. Most patients have complete resolution of symptoms within six months, as is illustrated by the next case.

Case 2

A 52-year-old unmarried teacher developed intermittent pain in her "tailbone" over a two month period. It was worse on sitting but there was no dysuria, vaginal discharge or pain with defecation. She was not sexually active. After a bus tour of the Southwestern United States she presented for evaluation. Height was 5′4″ (162.6 cm), weight was 114 lbs (51.3 kg); she appeared healthy. There was exquisite coccyx tenderness on palpation both externally and internally during the rectal examination. Pelvic examination was normal; there was no rectal mass; stool was guaiac negative. Coccyx x-rays were unremarkable. The patient was relieved to hear that her examination was normal. She used a foam rubber doughnut and naproxen 250 mg by mouth twice daily. The pain resolved over the next month and she has been pain-free during five months of follow-up.

Comment: Subacute trauma, usually not recognized as such by the patient, is the second most common etiology of coccydynia. This patient probably traumatized her coccyx during her long bus ride. A complete history and physical examination excluded any worrisome pathology and the diagnosis was confirmed by careful follow-up. This patient was at particular risk for coccydynia because she is so thin. Pilonidal cyst or infections, such as salpingitis or perirectal abscess, can cause coccydynia, but our patient was not at risk for sexually transmitted disease, and pelvic and rectal examinations were normal. Proctalgia fugax can mimic coccydynia, but these patients will have no coccyx tenderness on examination.

Levator ani spasm can contribute to coccydynia and has been treated with digital massage through the rectum, or injection of local anesthetic with or without cortisone.[3, 4] Surgical removal of the coccyx was frequently performed during the nineteenth and early twentieth centuries,[2] but is rarely used today because simple conservative measures such as a foam doughnut and analgesics are usually sufficient to relieve coccygeal pain.

Case 3

A 22-year-old medical student developed coccygeal pain shortly after riding his motorcycle from Houston to Mexico City and back, a distance of 2000 miles (3225 km). Physical examination revealed coccyx tenderness but was otherwise unremarkable. He was advised to sit on a pillow, but only complied during the evening because he was embarrassed to carry a pillow to class. He continued to ride his motorcycle against his physician's advice. Ultrasound treatments did not relieve his pain, and an injection of local anesthetic made it worse. The pain persisted for 9 months; he sold his motorcycle and in 14 years of follow-up he has not had a recurrence.



Figure 3. *Case 3, a 22-year-old man with coccydynia from motorcycle riding. The slumped sitting posture exacerbates the condition by shifting weight from the ischial tuberosities and thighs onto the coccyx.*

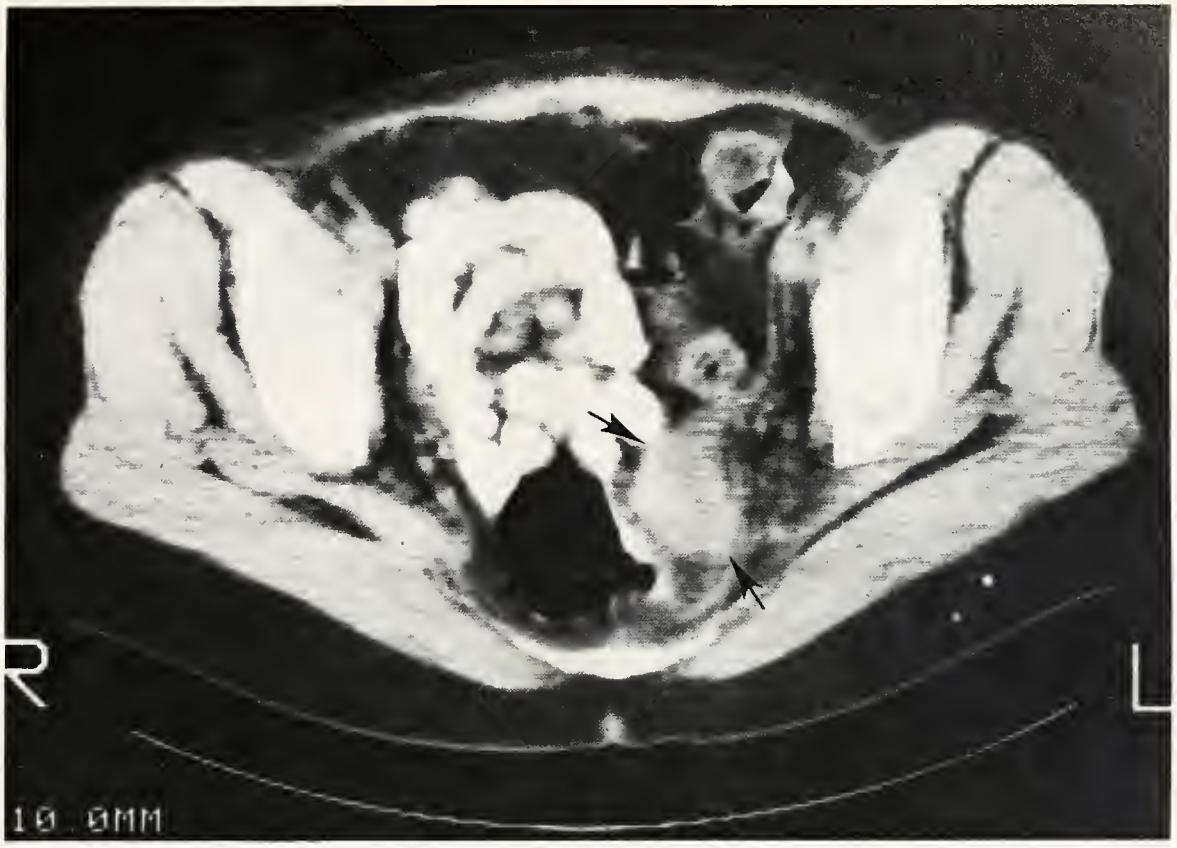


Figure 4. *Computerized tomography of the pelvis from Case 4. Arrows indicate the presacral mass due to metastatic endometrial cancer which caused coccydynia by nerve root involvement.*

Comment: In men with coccydynia, acute and chronic coccyx trauma can usually be identified. This patient sustained repeated blows to the coccyx from his motorcycle seat; men who ride tractors, jeeps or snowmobiles are also at risk.[4] Poor sitting posture contributes to the condition. This patient sat for long periods of time because he was a medical student, and he often sat in a slumped position (figure 3), producing direct pressure on the coccyx. Prolonged sitting while watching television can exacerbate coccyx pain, so one author has called coccydynia "television bottom."[4]

Most patients with coccydynia have a short-lived or benign intermittent course, but rarely a patient will present with more serious pathology, as is illustrated by the following case.

Case 4

A 50-year-old woman reported that she had fallen and dislocated her coccyx 20 years ago; she had improved spontaneously within several weeks. She was asymptomatic until four weeks prior to evaluation when she noticed the insidious onset of severe pain in her coccyx. There was no known trauma to the region but her job required that she sit for long periods. On examination there was tenderness at the sacro-coccygeal junction; no mass, redness or swelling was seen. On rectal examination movement of the coccyx induced pain but no mass was noted. Coccyx x-ray showed her old dislocation; bone scan was normal. She was advised to use a rubber doughnut and ibuprofen which helped minimally. Over the next two months the pain became increasingly severe. A repeat pelvic and rectal examination revealed a 2 cm tender, firm area along the left sacral prominence. Computerized tomography of the pelvis showed a left presacral mass (figure 4). Exploratory laparotomy revealed metastatic endometrial carcinoma invading the sacral plexus. After this lesion was removed the coccyx pain resolved. Unfortunately, the patient had a progressive downhill course and died nine months later.

Comment: Primary tumors involving the coccyx are extremely rare. Bone can be destroyed by cordomas or giant cell tumors; nerve tissue can be involved in ependymomas or glomus tumors of the cauda equina. Tumors of the pelvic organs as well as malignant melanoma and cancer metastatic from other sites should be suspected if coccygeal pain is markedly severe and unrelenting.[3] In such cases, pelvic and rectal examinations should be repeated and ultrasound or computerized tomography should supplement the clinical examination.

Plain coccyx x-rays are not helpful in most patients with coccydynia: in one series, coccyx x-rays were nondiagnostic in 95% of cases.[1] Plain films are primarily useful for detecting a fracture or dislocation; an enema to remove rectosigmoid stool prior to x-ray will give the best visualization of bony structures. In our patient, the plain films were unremarkable even though a tumor was present.

Summary

When the patient presents with a painful tailbone, the doctor should suspect that there is a small chance of malignant or infectious pathology. A good history and physical examination with close follow-up will generally rule out more serious disorders. When treated with proper posture, a doughnut cushion to relieve coccygeal pressure and a nonsteroidal anti-inflammatory agent, pain will improve or resolve within several months. If pain is progressive or unrelenting, further investigation is required.

Acknowledgment

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INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli, P. mirabilis, Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

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SCIENTIFIC ARTICLE

The Bedside Evaluation of Orthostatic Hypotension

Scott R. Brazer, M.D.

• *Simple, readily available bedside tests can narrow the differential diagnosis of orthostatic hypotension with little expense to the patient.*

WITHOUT a functioning baroreflex arc to maintain cerebral perfusion upon assumption of the upright posture, presyncope and syncope result. Patients with lesions at any point in that arc come to medical attention because of orthostatic hypotension.* In the 40 years since Dr. E. A. Stead Jr.'s review,[2] the differential diagnosis facing the clinician has become so extremely large that indiscriminate and expensive testing may result.

Case 1

A 35-year-old woman referred for evaluation of disabling orthostatic hypotension, had a supine blood pressure of 108/72 with a pulse of 100 while her standing blood pressure was 70 by palpation with a pulse of 160. The remainder of her physical exam was normal. The following studies, suggested by numerous consultants, were either "negative" or normal: rectal biopsy; sigmoidoscopy; upper GI with small bowel follow through; myelogram; liver spleen scan; brain CT; chest x-ray; urine metanephrine/VMA; serum protein electropheresis; lumbar puncture (×2); serum cortisols; angiotensin converting enzyme; toxin screen; chem 18; thyroid panel; FANA (×2); CBC; urinalysis; VDRL (×3); sputum AFB culture; urine Bence Jones protein; urine porphyrins; stool porphyrins; urine porphobilinogen; free erythrocyte protoporphyrin (the latter four tests ordered after a false positive screen); urine for heavy metals; and 48 hour ACTH stimulation test. Hospital costs exceeded $20,000. Yet the cause of her disorder was not clarified. She was discharged wearing a Jobst garment, eating a high sodium diet, and taking fludrocortisone but was able to walk only short distances with assistance.

The first issue to address in patients who present with orthostatic hypotension is whether the baroreflex arc (figure 1) is intact and if not which component is not functioning properly. The integrity of the entire system and the function of the individual components may be sequentially examined, much as an electrician tests a faulty circuit, giving appropriate direction to the subsequent diagnostic work-up. The elaborate or invasive testing of these patients, characteristic in the 1940s-1960s, may be avoided in most clinical settings and can be replaced by simple bedside maneuvers. Although intravascular recordings are more accurate in determining blood pressure, noninvasive monitoring is preferred because of increased patient comfort, elimination of risks, decreased cost, and because it does not cause the marked alterations in response of the baroreflex arc to orthostatic challenges, seen with intravascular monitoring.[3]

The integrity of the entire circuit can be tested with an electrocardiogram (ECG) rhythm strip and two simple maneuvers.

Paced Respiration. The patient breathes deeply at a rate of six times a minute. A normal response is defined as an

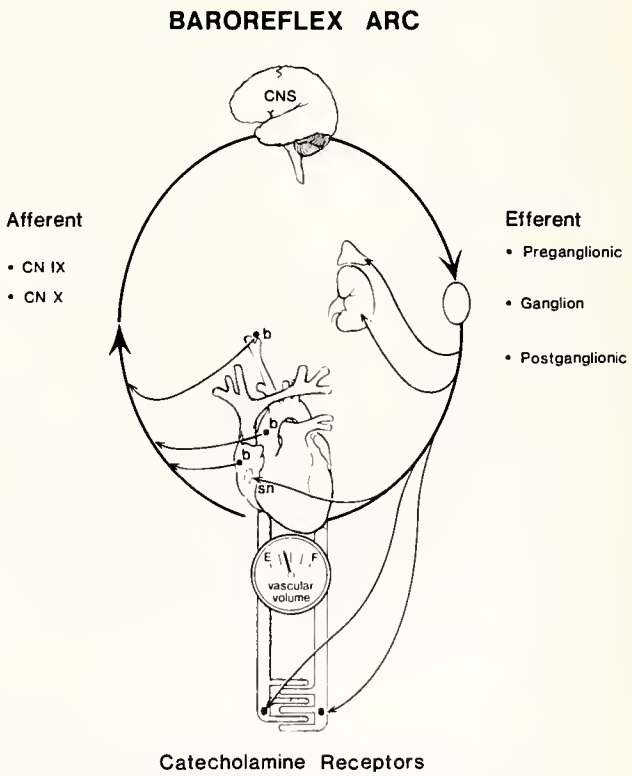


Figure 1. *The baroreflex arc.*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

* Arbitrarily defined as a systolic BP decrease of 30 or a diastolic BP decrease of 15 recorded at one and two minutes after assuming an upright posture in a symptomatic patient.[1]

increase in pulse of greater than 15 on inspiration; an abnormal response results in an increase of less than 10 beats per minute.[4]

Valsalva Index. The Valsalva maneuver has four phases, the first two during strain and the second two after release: I. increased blood pressure secondary to increased intrathoracic pressure upon the aorta; II. decreased blood pressure and resultant tachycardia secondary to decreased venous return and cardiac output; III. further decrease in blood pressure and tachycardia secondary to release of intrathoracic pressure on the aorta; IV. so-called "overshoot" of blood pressure with bradycardia secondary to vasoconstriction induced in phases II and III.

While the ECG is being recorded, the patient performs a Valsalva maneuver by blowing the mercury column of a sphygmomanometer to 40 mm Hg for 15 seconds. The ratio of the longest RR interval in phase IV (after release) divided by the shortest RR interval in phase II (before release) should be greater than 1.2. A ratio less than or equal to 1.1 is considered abnormal.[4]

If these tests are normal, the individual's reflex circuit is intact. Such patients have postural tachycardia as well as elevated catecholamine levels and have sympathicotonic orthostatic hypotension or intravascular volume depletion (technically a secondary form of sympathicotonic orthostatic hypotension).

Sympathicotonic orthostatic hypotension occurring in euvolemic patients is a result of an insufficient increase in the vascular bed's tone. The cause of the primary form, usually a disease of young females, remains unknown. Secondary sympathicotonic orthostatic hypotension occurs in patients with severe illness typically from infection or with profound electrolyte disturbances.

If any of the screening tests are abnormal, the circuit is not intact. These patients have hypoadrenergic orthostatic hypotension and commonly have other features of autonomic insufficiency such as impotence, decreased sweating and loss of premonitory signs prior to a faint. Their prognosis is less favorable than patients who have an intact reflex arc.[5]

One can bypass the afferent limb and test the efferent limb in such a patient by the cold pressor test. Placing that individual's hand in ice water for one minute should cause a rise in systolic blood pressure greater than 15 mm if the efferent limb is intact.[6] A normal response then implies an afferent limb defect.

If the cold pressor test is abnormal, the efferent limb is defective. Postganglionic lesions can be defined by their resultant denervation hypersensitivity. For example, instillation of 1 or 2 drops of 1 : 1000 epinephrine into the eye of such a patient often produces marked dilation whereas this dose would lead to no significant pupillary change in normal individuals. In addition, patients with postganglionic defects have low plasma norepinephrine levels, another aid in distinguishing them from those with preganglionic efferent defects.

Case 2

A 57-year-old man who had recently undergone resection of a posterior fossa astrocytoma presented with presyncope due to orthostatic hypotension. Supine blood pressure was 174/120 with a pulse of 76 while standing blood pressure was 94/70 with a pulse of 84. He had an abnormal response to paced respiration (pulse change of 6); an abnormal Valsalva Index (1.0); and the cold pressor response was absent (figure 2). These findings localized the defect to the efferent limb, consistent with a preganglionic lesion resulting from prior surgery and the tumor per se. Therefore, no further diagnostic testing was necessary. In this instance the evaluation took less than 15 minutes with a cost of only $20 for the ECG.

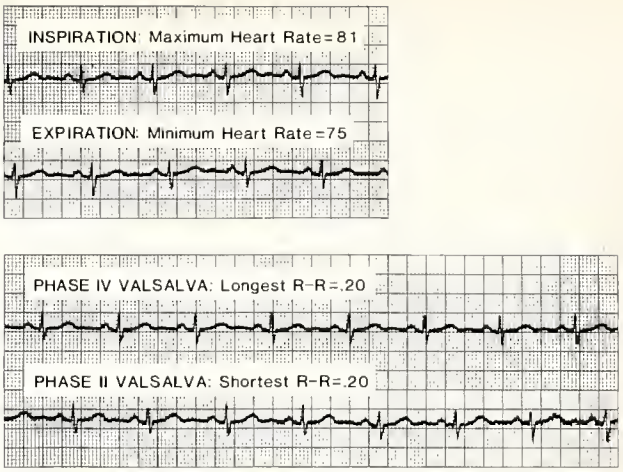


Figure 2. *Results of paced respiration and Valsalva Index in case 2.*

Later re-evaluation of our first patient after the initial exhaustive studies, showed an intact reflex circuit manifest by normal responses to Valsalva and paced respiration. One could have eliminated from the differential those diseases which result in destruction of the baroreflex arc from these screening tests alone. The etiology of her illness was still unknown 3 years after the onset, when she had recovered sufficiently to return to work. She is typical of patients with primary sympathicotonic orthostatic hypotension.

Treatment

Whenever possible, the underlying disorder should be treated. When that is not feasible or doesn't eliminate the patient's symptoms, the next step should consist of mechanical maneuvers which are relatively inexpensive and carry little risk. Patients should be instructed to rise slowly from a supine or sitting position. Sleeping with the head of the bed elevated may activate the renin-angiotensin system, thereby decreasing the amount of venous pooling that ordinarily occurs upon arising. An elastic garment, properly fitted from the metatarsals to the costal margin, is frequently helpful. Bannister[7] has described the vicious cycle of orthostatic hypotension in which forced inactivity leads to further deterioration of the baroreflex arc. This phenomenon might be prevented by the use of a conservative exercise program when tolerated by the patient.

The pharmacologic approach to treatment includes volume expanders and vasoconstrictors, recognizing that these methods may precipitate recumbent hypertension or congestive heart failure. Cautious use of high sodium diets with fludrocortisone should be attempted in patients who

do not have contraindications. Remember, the recumbent hypertension induced by these agents can result in increased cerebrovascular resistance and thereby might aggravate symptoms of cerebral ischemia when assuming an upright posture.[8] Single case reports and collected series have suggested benefits from a variety of drugs including: ephedrine, vasopressin, tyramine, ritalin, amphetamines, phenylephrine, MAO inhibitors, dihydroergotamine, midodrine, inderal, pindolol, indomethacin, clonidine, yohimbine and metoclopramide.[2, 6-9] These agents have not met with widespread or lasting success and are often harmful.[7] They should therefore be prescribed only by those familiar with their use and with the need for serial observation since long-term complications often outweigh transient improvement.

Conclusion

The differential diagnosis of orthostatic hypotension is broad but can be narrowed with readily available and easily performed bedside tests (figure 3). Such an algorithm aids in the assessment of patients with the problem, and when the etiologic diagnosis is not readily apparent the subsequent work-up can be focused more precisely. An ECG, sphygmomanometer, bucket of ice, and some epinephrine ophthalmic solution are all that is needed to guide the evaluation and assign the disorder to a specific component of the baroreflex arc.

Difficulty may arise when employing this schema in patients who have lesions in more than one location. Most patients with idiopathic orthostatic hypotension have been noted to have their predominate lesion in the postganglionic efferent limb; but abnormalities of the afferent limb, preganglionic efferent limb and catecholamine receptor have been described. Diabetics may have orthostatic hypotension secondary to involvement of the afferent limb and baroreceptor, postganglionic efferent limb, or due to intravascular volume depletion.[10]

Patients with lesions involving the CNS or the vascular bed are confusing because our understanding of their role in blood pressure regulation is incomplete. With the development of centrally acting antihypertensives,[11] the CNS circuitry is becoming clearer. The afferent pathway of the baroreflex arc leads to the nucleus tractus solitarius in the floor of the fourth ventricle. Axons from this area run to the rostral ventrolateral medulla which acts as the vasomotor center. Its neurons synapse with the preganglionic efferent neurons in the intermediolateral column of the thoracic cord. As our understanding of the central nervous components improves, disturbances of them may be more accurately correlated with specific clinical diagnoses.

Orthostatic hypotension occurring in patients with an intact reflex arc is due to an inadequate response by the vascular bed to either the hyperadrenergic state or hypovolemia. One term for this is sympathicotonic orthostatic

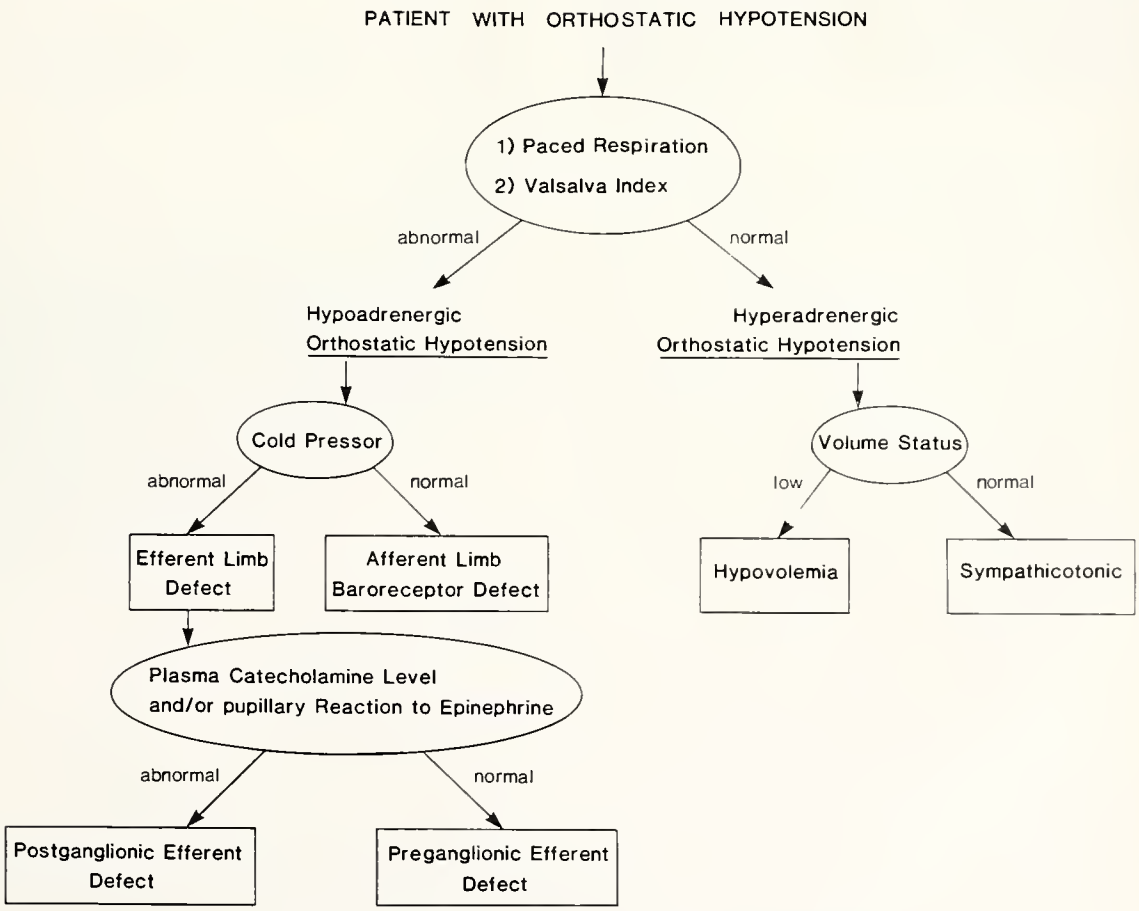


Figure 3. *Algorithm for evaluation of orthostatic hypotension.*

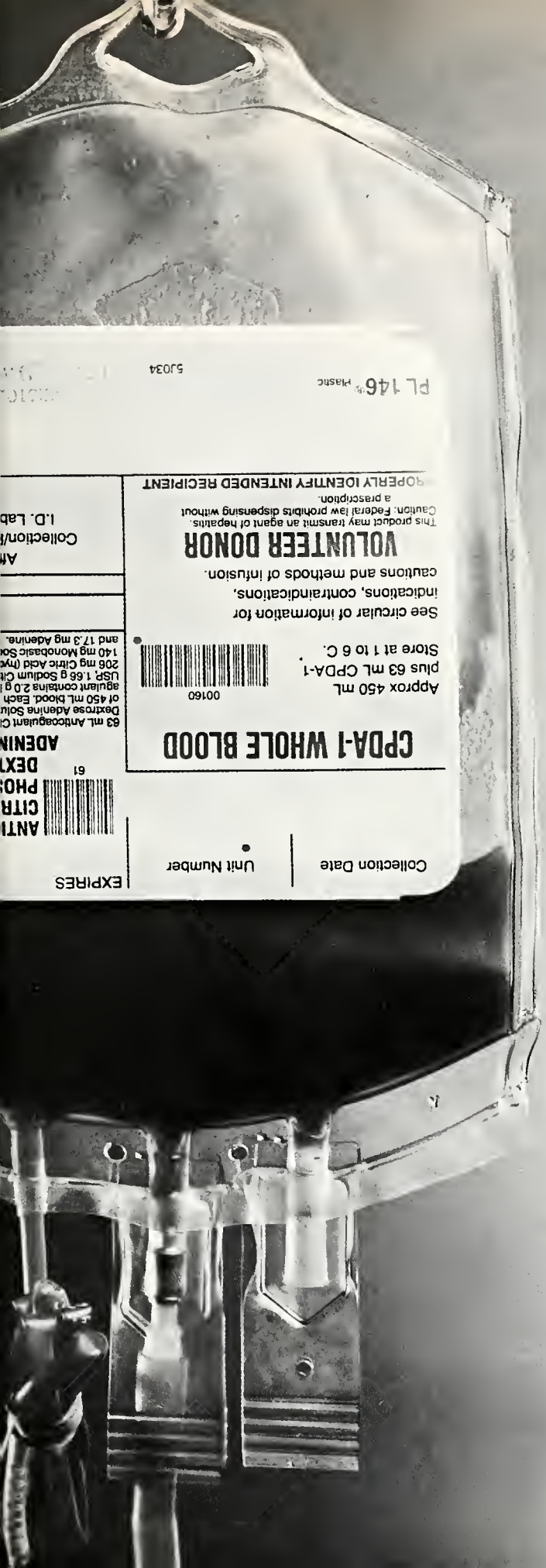
Table 1
Differential Diagnosis of Orthostatic Hypotension

Hypoadrenergic (arc not intact)	Hyperadrenergic (arc intact)
Postganglionic Efferent Defect 1. Neuropathies (i.e., alcohol, diabetes) 2. Idiopathic orthostatic hypotension 3. Sympathectomy 4. Sympatholytic drugs	Sympathicotonic 1. Primary 2. Secondary a. severe illness b. electrolyte abnormalities
Preganglionic Efferent/Central Defect 1. Destructive lesions (i.e., CVA, tumors) 2. Centrally acting drugs 3. Riley-Day syndrome 4. Shy-Drager syndrome	Hypovolemia 1. Absolute (i.e., Addison's) 2. Relative a. vasodilating drugs b. endogenous vasodilators 1) pregnancy 2) hyperbradykinism c. varicose veins d. prolonged bedrest e. pheochromocytoma
Afferent/Baroreceptor Defect 1. Diabetes mellitus 2. Alcohol 3. Hemodialysis related 4. Holmes-Adie syndrome 5. Tabes dorsalis	

hypotension. A primary form occurs as an idiopathic disorder most commonly affecting young women. Secondary forms are seen in patients with severe co-existent illness or hypovolemia. It is not difficult to understand the clinician's pursuit of a treatable condition in an otherwise healthy young patient disabled by orthostatic hypotension; however, demonstration of an intact reflex arc allows this search to be confined to those entities that cause orthostatic hypotension without destruction of the circuit (table 1).

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North Carolina Medical Journal

Features for Patients April 1985

Premenstrual Syndrome

John F. Steege, M.D., Anna L. Stout, Ph.D., Sharon L. Rupp, R.N.C.

Recently much attention has been given to an age-old problem: the changes that many women experience premenstrually. When these changes are more severe, they have been called "premenstrual syndrome" or "PMS." These pages will review what PMS is, how women can help themselves with the symptoms, and what kind of medical help can be most useful.

PMS — The Problem

Many women experience some feelings of breast tenderness, greater or lesser degrees of symptoms from fluid retentian, and some feelings of emotianal change. Many also experience positive feelings of increased energy, greater sensitivity both emotionally and artistically, and greater creativity for a week or two prior to the beginning of the menstrual flow.

From ancient times medical writers have described some of the more negative aspects of these changes and have puzzled over the causes. The impact of the menstrual cycle on the human body is profound. Approximately 65 well-recognized medical diseases and 115 normal events in the body's physiologic makeup have been shown to be influenced by the menstrual cycle. It is no wonder, then, that women who experience severe changes premenstrually may notice a wide variety of symptoms. Approximately 150 symptoms have been described at one time or another as being related to the menstrual cycle.

The symptoms of PMS can be grouped as shown in table 1. Our experience tells us that women who experience more severe emotional changes premenstrually do not necessarily experience physical changes that are more severe than other women. Rather, they find emotional changes extremely disturbing and disruptive in their personal relationships and their ability to function at work and home.

Although a great deal of research has been done, no one has really discovered the cause of PMS. Most peaple agree that it is a "real" illness, that definite chemical and physical changes are involved with PMS symptoms, but the exact nature of thase changes is unclear. Many others have recognized, however, that a person's individual personality and the stresses to which that person is exposed may have strong influences on the severity of PMS symptoms.

This complex disorder deserves a most careful evaluation in order to bring about the best results from any kind of treatment.

Making the Diagnosis

Many women can simply think back in time and accurately remember that every time their period approaches they will feel irritable and somewhat depressed. When they write down these events on a calendar the pattern is often confirmed.

However, when a person is troubled with significant premenstrual symptoms, making the diagnosis is often more difficult due to the way our memories work. When two events happen together, it is easier for a person to remember them than to recall similar events that occur singly. For instance, if someone has a migraine headache during the menstrual flow it has been shown that it is easier for her to remember those events together than it is to remember migraine headaches that may happen at other times in the cycle, when nothing else is going on.

For these reasons, most doctors or clinics working with PMS find it best to first find out what a woman's major symptoms are and then have her chart those symptoms on a daily basis using one type of calendar or another. She can then bring these calendars to the next visit with the doctor and examine them to see how much of the difficulty she is experiencing follows a premenstrual pattern. The doctor should also perform a thorough physical examina-

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Table 1
Common Symptoms of Premenstrual Syndrome

Affective	**Cognitive**
Sadness	Decreased concentration
Anxiety	Indecision
Irritability	Paranoia
Labile mood	Sensitive to rejection
Pain	Suicidal ideation
Headaches	**Neurovegetative**
Breast tenderness	Insomnia
Joint and muscle pain	Hypersomnia
Autonomic	Anorexia
Nausea	Craving for certain foods
Diarrhea	Fatigue
Palpitations	Lethargy
Sweating	Agitation
Fluid	Libido change
Bloating	**Central Nervous System**
Weight gain	Clumsiness
Decreased urination	Seizures
Swelling	Dizziness
Behavioral	Vertigo
Decreased motivation	Paresthesias
Poor impulse control	Tremors
Decreased efficiency	**Dermatological**
Social isolation	Acne
	Greasy hair
	Dry hair

From Rubinow DR, Roy-Byrne P. Premenstrual syndromes: overview from a methodologic perspective. Am J Psychiatry 1980;141:163-72.

tion to look for other medical illnesses that might influence a person's general feeling of well-being as well as perhaps be responsible for symptoms similar to PMS. Some screening blood tests to look for various kinds of medical illness are also useful. No one yet has discovered any single blood test to diagnose PMS. Various hormone levels including progesterone levels are useful in deciding whether the menstrual cycle is normal in certain ways, but none of them is accurate in diagnosing premenstrual syndrome.

There are several gynecologic conditions that can perhaps contribute to some of the symptoms of premenstrual syndrome, especially the lower abdominal and pelvic cramping and aching. These include endometriosis, large fibroids in the uterus, and a condition called adenomyosis which can cause some enlargement or swelling of the uterus. Often these problems can be detected on a regular pelvic examination, but they sometimes require a laparoscopy for confirmation. This minor surgical procedure, done under anesthesia, allows the doctor to look inside the pelvic area.

PMS can occur at any age after menstruation has begun. However, women are often most severely affected during their 30s and 40s. Although many clinicians have wondered whether such things such as having children, taking birth control pills, or having menstrual cramps (dysmenorrhea) influence women's tendencies to get PMS, most of these ideas have not been confirmed by research so far. For example, there is no credible evidence that taking birth control pills aggravates premenstrual symptoms with any regularity, nor do they make a person more likely to get severe PMS symptoms after discontinuing the pills. Similarly, although some women will note the beginning of PMS symptoms after childbirth, most do not seem to follow that pattern, or any other pattern relating events in reproduction (sterilization, etc.) to the beginning of PMS symptoms. It has been said that menstrual cramps are seldom present in women with PMS. Our experience has been quite contrary to this; we find that many women with more severe PMS also have more severe menstrual cramps. These examples are important to keep in mind since they demonstrate that we really need to know a lot more about premenstrual syndrome.

Another extremely important area in the evaluation of PMS is an assessment of an individual's overall personality and the stress that she might be experiencing in day-to-day life. We are just beginning to learn about the ways in which stress can affect a person both physically and psychologically, and we have known for many years that stressful things can influence the menstrual cycle in very profound ways, such as stopping the cycle altogether, or sometimes preventing the release of an egg from the ovary (ovulation). Often progress made in reducing the effect of the stresses in one's life can also bring about significant improvement in PMS symptoms.

Many doctors ask their patients with PMS to undergo some form of psychological evaluation for these reasons. This might involve psychological testing and almost always involves some kind of interview with someone experienced in the mental health or counseling field.

Causes and Treatments of PMS

We will discuss the causes and treatments of PMS together, since various ideas about causes have logically led to suggestions about how to treat the problem.

It is important to know that it is very difficult to prove that a particular medication or treatment is effective because of the very complex nature of the problem. Since there are no

bload tests to fallow to laok far improvement, we must rely on reports af changes in symptoms, many af which are internally perceived and cannot be observed by sameane other than the person affected. For these reasons, most studies loaking at drugs in the treatment af PMS will notice that anywhere between 25% and 50% af women will notice some improvement even with a placeba ar "sugar pill" medication.

Another majar factor in the difficulty in finding a "cure" far PMS is that it seems that combinations of treatments very aften work better than any single treatment by itself. This makes it very difficult far researchers to figure aut which might be the most important "ingredient" in a treatment. Nevertheless, we will review the treatments mast often used and discuss their value.

Nutrition

Many women camplain of distinct food cravings during their premenstrual time. Usually these are far sweet faods including such things as chocolates, cake, bread, and other carbahydrates. There is same evidence that the bady handles these products differently premenstrually than it does at other times. Diabetics more aften have trauble regulating their disease during this time and insulin productian is samewhat different premenstrually in wamen withaut diabetes. There is same thaught that hypoglycemia, ar the tendency af the blood sugar to drap down to a low level in a rebound fashion after a meal high in sugar, is mare comman in people with premenstrual syndrome.

Although nutritian in PMS remains incompletely investigated, there is same evidence to suggest that peaple with premenstrual syndrome symptams in fact eat a less well balanced diet than those without symptoms. For these reasons we and athers have faund it useful to suggest certain dietary madifications ta treat PMS.

We suggest that a person eat a diet with a normal protein level, with only small amounts af faods with high sugar cantent and refined carbahydrates. The "refined" carbohydrates are most commonly seen in white flour praducts and sweet faods in general. In addition, it is gaod to avaid chocalate because of both its high sugar content and its caffeine level.

Chemicals that stimulate the brain are alsa thaught to increase irritability premenstrually, especially substances such as caffeine. Using decaffeinated beverages is aften helpful.

Although many women repart feelings af bloatedness premenstrually, careful study has failed ta dacument significant weight gain premenstrually in mast women. Far this reason, we discourage the use of diuretics ar fluid pills, but do find it useful far a persan to be careful about avoiding excess sodium intake during the premenstrual time. This wauld mean avoiding salty faads such as preserved meats (bacan, sausage, ham, etc.), commercial vegetable praducts with salted sauces, broth saups, patato chips, etc.

Considerable attentian has been paid to the role of micranutrients ar chemicals that are present in small amounts in aur diets. We generally recammend a single multivitamin/multimineral supplement that is available in many farms at the vitamin caunter of the drug store. There is no gaod praaf that special supplements high in such things as zinc and magnesium have any additianal benefit in treating premenstrual symptoms.

Vitamin supplements are frequently recommended for PMS. Vitamin B_6, ar pyridaxine, has been known for many years ta be an important factor in many chemical reactions in the body including thase involving sugars as well as many brain chemicals thaught to influence maod. In additian, gaad studies shaw that vitamin B_6 will relieve depressian symptams in a significant number af women experiencing these problems while taking birth contral pills. Far these reasons vitamin B_6 has been used to treat PMS. There are several studies ta shaw it is effective. Most studies have used vitamin B_6 at 100 mg per day and for this reasan we stick to this dose level. There is real concern about toxicity to the nerves, that is, prablems with decreased sense af balance and touch, in peaple wha use mare than 2,000 mg daily. Althaugh there is no evidence suggesting taxicity at lawer doses, we have maintained the 100 mg per day limit out of caution. When a person uses vitamin B_6 supplements it is useful to use a general vitamin B complex supplement as well.

Vitamin E has been described as helpful far the treatment af breast pain premenstrually as well as for relief af pain from fibracystic changes in general. Although there is again same confusian in this area many physicians do feel it useful at a dase of about 400 units per day.

Exercise

Much research has been done recently abaut the effects of exercise on brain functian and mood in general. Good studies shaw that it is effective in treating simple forms of depressian, and other reports indicate that it helps the symptams of premenstrual syndrome as well.

Researchers have speculated that exercise changes the levels af brain chemicals called endarphins and that this may be important in both the regulation of maod and the perceptian of pain. For these reasans, as well as for the general feeling of well-being that exercise aften pravides, we suggest regular daily exercise for women experiencing PMS.

For many wamen PMS symptoms become mast bathersame during stressful times. Often this means that they feel unable to fulfill all their responsibilities at work and at hame. This is just the time when a prescribed break af even as little as 15 minutes ar one-half haur per day far a walk is very useful far caping with stress.

Exercise may alsa help combat the effects af sleep disturbance that sometimes appear premenstrually.

Altered sleep patterns that accompany PMS and depression may be the cause of some general muscle aches and pains and stiffness that people often report.

Finally, daily exercise will help with weight reduction. Some doctors feel that PMS symptoms are worse for women significantly over their ideal weight.

Lifestyle

Of the problems reported by our patients, the most common is the feeling of not being able to cope with ordinary demands. One of the most helpful things about charting one's own symptoms is that it becomes possible to predict on which days the most difficulties will be encountered. With this in mind, it may be possible to schedule some optional activities that are stressful for the times when the fewest symptoms are present. Certainly, this is not always possible, but to whatever degree it can be done, this plan can certainly be helpful.

One of the easiest suggestions to make, but perhaps one of the hardest to follow, is to allow a bit of time for yourself, even on the most stressful days. Whether this is in the form of simply being alone, having the time for a leisurely bath, a brief walk, or whatever activity is seen as relaxing, it can give a welcome respite from the feeling of being unable to cope. Other members of the family may be quite willing to take over for these brief periods when they see how helpful it can be.

Many couples find that they have disagreements which repeatedly emerge during premenstrual times. Often the discussion becomes heated to the point where productive problem-solving cannot take place. In such situations, often the best thing a couple can do is simply agree to stop the discussion with the agreement to return their attention to the issue at hand when moods are calmer, perhaps in the first half of the next cycle. It is important, however, that the issues raised premenstrually not be dropped entirely or dismissed as being unimportant. Rather, more useful problem-solving can be undertaken when both people can approach the issue more calmly.

Some couples have found the premenstrual time to be useful to them in a very positive way. They find that the increased feelings of sensitivity at this time can make them aware of disagreements or issues between them that they might not have otherwise been able to detect. They can then use this insight for understanding their relationship better and helping it to continue to grow as time goes on.

Hormonal Treatments

Much has been said and written about the role of hormones in causing premenstrual symptoms. Most scientists now feel that there are different chemical changes that cause premenstrual symptoms, but these changes are likely to involve chemicals in the brain rather than hormones produced by the ovaries. Specifically, no convincing evidence has turned up to say that PMS is caused by a simple deficiency of one hormone or another, such as progesterone.

Nevertheless, hormonal treatments have been used effectively as medications (not as replacements for a "deficiency"), and are often employed when the measures described so far are not sufficiently helpful. The two general types of hormone treatments that are used are those that 1) eliminate or suppress a woman's own hormone cycle, perhaps replacing it completely with hormones taken as medication, and 2) add to or supplement a woman's own hormones.

In the first group, those treatments that eliminate a person's own hormone production, are oral contraceptives (birth control pills), continuous use of medroxyprogesterone (a synthetic progesterone-like compound), hysterectomy with removal of both ovaries, estrogen implants with the periodic use of progesterone either in the form of regular progesterone or medroxyprogesterone, and finally recent experimental work with a hormone called GnRH agonist, which works at the brain level to shut down a woman's own menstrual cycle. We would like to say a little about each of these individually.

It has been known for many years that oral contraceptives will reduce premenstrual syndrome symptoms in general. However, some women with more severe premenstrual depression before going on the pill stand a greater chance of that depression worsening if they try the pills for contraception. About half of women who notice worsening depression on the pill will have that depression relieved by taking about 50 mg of vitamin B_6 daily. Perhaps because of the worsening of depression in some people and because of some other general concerns about the pill, it has been suggested that the birth control pill will always aggravate PMS symptoms. This is not the case, and the pill remains a useful form of treatment for some women. There is no evidence that being on the pill makes a woman more likely to get worse PMS symptoms after discontinuing it. In our own clinic, we suggest the birth control pill for those who have experienced no negative side effects from it in the past and for whom no other contraceptive method is as appropriate.

Medroxyprogesterone acetate (Provera), is the drug that has been used for many years to regulate episodes of irregular bleeding. Its actions are very similar to those of regular progesterone and it can be taken by mouth. For this reason it has been used by some clinicians to treat PMS, but apparently with mixed success. Although several studies show no effect of this compound on PMS, numerous clinicians have reported that some people do quite well on it while others find that their depression is aggravated by it. Our experience agrees with this and we recommend it only occasionally. We discourage the use of the injectable form

of medroxyprogesterone acetate due to the fact that it will remain in the system for 3-4 months after each injection. If any negative side reactions take place it can take a long time for the drug to be eliminated from the body.

Removal of the ovaries certainly brings about some relief of PMS symptoms in some physicians' experience. However, there are no published reports documenting this, and most clinicians feel that this is rather drastic treatment for a disorder that can be quite effectively treated medically. Also, following removal of the ovaries, replacement hormones are necessary to maintain proper bone strength and proper lubrication capacity of the vagina as well as to eliminate hot flashes. These hormones will sometimes bring a return of some of the symptoms of PMS, although usually to a less severe degree.

In England, several physicians have used implanted pellets containing estradiol, an estrogen compound, to treat PMS. In order to prevent a precancerous overgrowth of the lining of the uterus (endometrial hyperplasia), they need to give progesterone or a progesterone-like compound for 10-14 days out of each month as well. This regimen essentially replaces a person's own hormone cycles with those provided by the medications and seems to treat PMS quite effectively. However, when the cyclic use of a progesterone-like compound is given as well, some of the PMS symptoms seem to return. This medication has not been proven safe for general use and is not available in this country.

Finally, recent work with gonadotrophin-releasing hormone (GnRH) agonist has demonstrated once more that if you shut down the function of the ovaries, premenstrual symptoms will disappear. However, this is very preliminary work and it is not available or recommended for general use as a treatment for PMS. There are significant problems that remain to be worked out with this treatment, especially the possibility of osteoporosis, or weakening of the bones, due to estrogen deprivation while on this treatment.

In general, although the treatments listed above are somewhat effective, they work by eliminating the menstrual cycle rather than adjusting or treating it in order to control symptoms. Our philosophy is that this is perhaps more meddlesome than hormone supplementation therapy as described below.

Dr. Katherina Dalton of England has been the most vocal proponent of progesterone supplementation therapy for treatment of PMS. There is now a growing experience in this country with this medication including the work done in our clinic. Although truly accurate studies have not been done to show that progesterone is more effective than a placebo, many clinics using progesterone find that the apparent effectiveness of the medication seems to last much longer than the 2-3 months one would expect a placebo to last. While awaiting further scientific studies to demonstrate its role, many clinics are continuing to use it in one of several forms.

Progesterone supplementation therapy is usually confined to the second half of the menstrual cycle, starting at or around the time of ovulation and continuing until approximately day 27 or 28 of the cycle, just before the anticipated menstrual flow would begin. It can be given in one of several forms: rectal or vaginal suppositories, a fluid used rectally as a "micro enema," drops placed under the tongue or injections.

A number of different types of suppositories are available, but some recent evidence suggests that the best absorption is obtained using polyethylene glycol (PEG) base suppositories. Although these are somewhat inconvenient and sometimes messy to use, most PMS sufferers find that they can become accustomed to using them either rectally or vaginally or alternating between these routes. We have found quite good results using between 200 mg and 400 mg per day divided into two doses with the PEG base suppositories. Our limited experience in seeing patients using higher doses indicates that they did not reach significantly higher blood levels with very large doses. Promising research is currently going on to investigate a way of delivering progesterone via nasal medication.

It is important to keep in mind when using these various hormonal measures to treat PMS symptoms that they are being used as medications to treat symptoms and not as the replacement for a known hormone deficiency. In this light, one might reach a point when other measures become more effective and hormone therapy is no longer required.

Other Medications

Aside from the hormonal and nutritional medications already mentioned, numerous other drugs have been used. We mentioned briefly that diuretics, or fluid pills, are widely used although they have no proven benefit. The only diuretic that has any evidence supporting its effectiveness in PMS is spironolactone. Used in amounts between 50 mg and 100 mg daily, some women find it effective. We generally have used this only when true weight gain has been documented by daily records, in order to avoid the possible hazards of dehydration from excess diuretic use.

Drugs that affect a person's emotional or psychological status, or psychoactive drugs, have also been used. These include many of the commonly employed anti-anxiety drugs and antidepressants. Although there are no controlled studies of these drugs in PMS, we have found them useful in several ways. First, drugs for anxiety can be used on an intermittent basis especially if a person's most severe symptoms are limited to only a few days before the onset of menstrual flow. This allows significant benefit with minimal chance for developing a physical addiction to the medications or a tolerance that

would lead to the use of high doses. Some of these drugs do make a person feel a bit sleepy and therefore when symptoms last longer than just a few days, many women find that they feel more comfortable using progesterone than they do putting up with the sleepiness for a week or two at a time.

The last group of drugs in comman use is the antidepressants. We have faund it useful to use antidepressants primarily when there is some evidence of depression all month long which gets worse premenstrually. We sometimes then use antidepressants in combination with progesterone, a combination which seems to wark better than either drug by itself. We employ this combination only with psychiatric consultation.

Counseling

Many women experiencing premenstrual changes find that over months and years of having symptoms, their lives and relationships have been gradually eroded or damaged. Even when symptoms are improved with appropriate medication, they still find that they have a significant amount af recuperating to do in an emotional sense. For this reason, many individuals and couples find it helpful ta take advantage of the benefits of individual, family, or couples therapy in addition to some of the medication treatments for PMS.

Premenstrual symptoms can also happen along with ather disorders such as anxiety disorders, panic disorders, continuous depression, and manic depressive illness. It is sometimes useful to cambine both medical and psychological treatments for these problems with some of the treatments described above. It often works out best if the physician or other health care provider responsible for PMS care has a good working relationship with one or more people in the counseling fields.

Support Groups

Women suffering from PMS in many cities throughout the country have gathered together to form support groups. These groups meet an a fairly regular basis to share their experiences in attempting to cope with PMS symptoms, and to share hints on dietary adjustments, exercise programs, problem solving techniques in their relatianships, and finding appropriate sources of medical care. Such groups can be a very valuable source of emotional and practical help in dealing with symptoms associated with PMS. They can also assist a woman in deciding when her symptoms are serious enough to require more comprehensive evaluation and treatment.

Several national groups maintain a raster of support groups and also of sources of medical care for PMS. These include the National PMS Society, 3514 University Drive, Durham, NC 27707; and PMS Action, P.O. Box 19669, Irvine, California 92713.

Medical Care for PMS

The essentials of evaluation, in our view, are 1) prospective daily ratings of symptoms, ideally by the person affected by PMS and by her partner or someane who is close to her, and 2) some assessment of personality, relationships, and general stresses and strains in life. When symptoms are not very severe, and/or when a physician knows the patient well, this can be effectively carried out in the primary care physician's office. When symptoms are more intense, or when more comprehensive evaluation seems appropriate, referral to a center with an established evaluation program may be helpful, with a plan ta return to the primary care physician for followup care at an appropriate time.

Summary

There is now a growing recognition that premenstural changes are real, that definite (although poorly understood) chemical changes probably do account for many premenstrual symptams and that medical diagnosis and therapy are therefore indicated. At the same time, most clinicians dealing with premenstrual syndrome and many women affected by it also recognize that there are many ingredients in the mix, many factors that affect how a person feels premenstrually. Until we understand a bit better the exact nature of the problem, it seems best to assess as best we can the various ingredients or contributing factors and apply treatments that seem most appropriate for each one.

Hormonal and other drug treatments are very helpful. They are most effective when used together with the diet and lifestyle changes previously mentioned. If life stresses can be reduced and unsolved problems worked out, it is sometimes possible to discontinue these medications and maintain symptom relief with the non-medication methods. Counseling or therapy is useful for many.

Finally, there is more hope now than ever before for women experiencing severe PMS. Many treatments are now available, and our understanding of the problem is growing as more and more research is done in this very important area of women's health care.

Sources of care for PMS associated with medical centers in North Carolina are

Duke Premenstrual Syndrome Clinic
Box 3308
Duke University Medical Center
Durham 27710
919/684-5322

Premenstrual Syndrome Clinic, Division of Reproductive Endocrinology
Department of Obstetrics and Gynecology
North Carolina Memorial Hospital
Chapel Hill 27514
919/966-5026

James L. Mathis, M.D.
Department of Psychiatry
East Carolina University School of Medicine
Greenville 27834
919/757-2660

Alive But Not Living

Eugene A. Stead, Jr., M.D.

Mac Mauney and I independently flagged the article in the February 8, 1985 issue of *JAMA* entitled "Just Alive, Or Living" for use in the *North Carolina Medical Journal*. I quote the paper in its entirety:*

"There are those, particularly in the medical profession, who would state that 'just alive or living' are the same conditions, but they are not. We who live in nursing homes (as I do at age 81) see all too vividly the difference between the two states of existence.

"I hasten to say that I am not a morbid person. I do not entertain an unhealthy death wish, nor do I advocate euthanasia. I still love living, even with all of its present restrictions, its many disappointments, and, too often, its painful times. The beauties of Nature, even seen through blurred vision, still delight me. I still thrill to a beautiful sunset and look on it as a wonderful harbinger of something good ahead and not just as an ending of another day.

"I treasure the good and interesting things in life and would like to feel I can enjoy them to the end, but the choice is not mine any more than it is the choice of the people I see about me to be bedfast or tied in a wheelchair. Some are no more than vegetables, but not from choice. Some have been lawyers, judges, teachers — and, yes, physicians. Their hearts beat and they breathe with or without the help of oxygen. So yes, they are alive, but one can hardly call it living. Of all of mankind's emotions, sometimes anger and sorrow seem to be the only ones left. Day after day and week after week these people just exist. They have become shells that house the spirit and nothing more. Time means nothing to them.

"Perhaps Nature has a better plan. I remember summers on the farm when I would find a cicada in its shell, clinging to the bark of a tree. Sometimes it would be there for a few days, but there would come a morning when I would find the shell split and the insect gone. The shell had finished its purpose for being.

"Medical science is a marvelous thing, and its forward strides are almost unbelievable. I would hope that research could go on and on, finding ways to help people have better and healthier lives. This, of course, particularly relates to prenatal through adult life, as long as there is still hope for a life that is meaningful to the person. I have a very deep interest in a large children's hospital and follow its reports of progress. If many of the things considered common practice today had been available at the time we elderly people were young, our whole lives could have been different.

"There was a time when pneumonia was called 'the old folks' friend.' When body functions had failed, pneumonia often gave the *coup de grace*. But today, antibiotics can bring these persons back from the very brink of death. But back to what? One can hardly call being fed, bathed, clothed, and changed and knowing nothing at all really living.

"I have been told that physicians take the Hippocratic Oath that describes the duties and obligations of a physician to maintain life. Isn't that carrying tradition rather far? I am sure you are not using the methods used by Hippocrates in 400 BC. If he could come back today, I wonder if he would not be horrified to see how patients who are really dead to all that means living are kept in a state of existence by the help of machines. Maybe the Oath needs some revising. It is hard to think of anything else that many centuries old that is still in use.

"We owe so much to science and to the physician's application of science. It has helped us travel in greater comfort over many of the rocky roads of life. Alleviation of pain is so greatly appreciated and certainly allows us to enjoy living in ways that would be impossible if every waking hour was just more time to endure pain. No patient can ever adequately express to his or her physician what real, kind help means to those who are ill.

"But there comes a time, a time when our bodies and too often our minds just wear out. Organ replacement for the elderly becomes a little like placing new parts in an old television. That part may work, but it isn't long before some other part wears out. At best you are only buying a little time for the patient — time for what? By the time we have reached our 80s and 90s, surely we have made whatever contribution to life that we are capable of, and I doubt that many of us could do it the second time around.

"Please! When all vital signs show the end is near, unless very drastic measures are taken, let us go. Prolonging a life for a person whose mind and body no longer function is an achievement for the physician, but do ask yourselves whether you are doing the patient any kindness.

"I just hope that I won't be alive any longer than I can live — but I will not be doing the choosing when that time comes."

Mauney, in his letter to me, says, "The simple, but eloquent, prose that this writer uses to make a statement about life and death values is so eloquent that I think it deserves reprinting in our *North Carolina Medical Journal*.

"Personally, I have espoused Lola Armstrong's viewpoint for many of my professional years. She simply has made me feel better about what I have tried to do professionally. The 'choice' is clearly the physician's and not a court of law. The responsibility

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* The author is Lolo M. Armstrong of Lawrenceville, Illinois. Reprinted with permission from JAMA 1985; 253:789.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

of the decision mandates that that physician will have taken the time and made the effort to know his patient's life values and philosophic viewpoint, as well as his or her 'symptoms and signs'."

At the time these papers crossed my desk I was preparing a response to a paper by Elaine Brody entitled "Institutional Versus Home Health Care of the Elderly." My theme was that the time has come to recognize the dementia of partial brain death as the beginning of the dying process and in proper circumstances to make no attempt to prolong life by influenza vaccine, antipneumococcal vaccine, antibiotic, feeding and drinking beyond what the person can do for himself. I wrote as follows:

"It is easy to be a good citizen until one reaches the age where dependency overtakes us. We have not yet found an easy or graceful way for most of us to leave the stage on which we performed adequately as independent persons.

"The question is what to do. I know of no way to make dependency as attractive as independence. The devotion of all our resources to the care of the dependent elderly would not make old age as attractive as youth.

"We have to face a most difficult issue: what level of care do we want to give to what groups of persons? Professionals in aging have rarely faced this problem directly. They want more of everything and would have the surroundings and personal services equal to those of the independent population.

"We have accepted that comatose persons who have dead brains may be declared dead even though circulation and respiration can be maintained. Will we in time accept dementia as slow dying, and when it disconnects the patient from his surroundings will we make no attempt to prolong life? In a demented person, what is the purpose of the medical procedures, the administration of food and water, the use of antibiotics, the daily vitamins, the polypharmacy? It is not to help the patient enjoy life. Too much of the brain is dead. We care for the partly dead person because we have not developed an ethical or religious system that allows us comfortably to call it quits. We are afraid that we will become dehumanized if we don't postpone death. The care is for the living and not for the dying. We face the same issue with birth control and abortion. The egg, sperm, and embryo never complain. It is the feelings of the persons who live that are at stake.

"When I have cockroaches in my living quarters, candy in every nook and corner, a refrigerator filled with rancid food, and have stopped bathing, I won't care. My children will be appalled and want to instigate change. They are afraid I'll break my hip and die before I'm found. If I'm institutionalized, what is the minimal acceptable care that society can offer?

In the old days it was simpler. In 1930 Dean Wilburt Davison, a renowned pediatrician, came to the medically under-served Southeast. He was in great demand as a consultant who could work out a care plan for demented children who placed heavy demands on the family and community. The consultation had some aspects of a festive occasion. When Dean Davison got down to business, he requested everyone except members of the family to leave. He then determined who was going to contribute personal services or money for support of the child. He asked all other family members to leave. The final hard choices were then made by persons who had to implement them from their own resources.

"In our day the family is not dependent on their own resources. They have a variety of community, state and federal resources to cushion them. Insurance coverage, Medicare, Medicaid, state and community agencies dilute the feelings of personal responsibility. If we let patients finish the act of dying without intervention we must ask ourselves: are we letting demented persons die because we don't want to pay more taxes? Are our actions moving us to tolerate a new holocaust because there is no ethical basis for non-intervention?

"It is interesting that we have devised cultural and ethical systems that allow us to kill millions of healthy persons without feelings of guilt. We have a name for that system. We call it war. Until we have a philosophical and ethical system which accepts death as a part of life and acknowledge that the last part of living is the first phase of dying, we will make no progress. How will we develop an ethical base for new types of behavior? I assume that it will come about by forces tangential to problems we are discussing today.

"Two changes in our culture have occurred by a tangential approach. Knowledge that cancer is caused by exposure of our bodies to a variety of chemicals has changed much of our behavior. You no longer have to put out ash trays when doctors congregate in large groups. Workers in chemical plants are forcing management to adopt new methods of reducing exposures. Years ago no one thought that prevention of cancer would be possible and that prevention would produce major changes in our lives. Cancer is now recognized as the work of man on biological systems. It is no longer an act of God.

"Eventually a new generation will come to believe that there are limits to the amounts of money and services they are willing to expend for the dying section of the population. The concept of partial brain death and ways to deal with it will emerge. By one device or another a system of behavior compatible with this belief will evolve, and society will permit the partially dead to complete the act of dying in peace.

"Meanwhile we struggle with the economics of home and institutional care. I've no objection because we must fill in time while forces that we have not yet anticipated mold our attitudes."

Living is not simple but in our society dying may be even more difficult.

Taljaribu Kila Dawa Isifal: Yohimbine Intoxication

Ronald B. Mack, M.D.

• *Yohimbine, a new street drug, comes from the bark of a tree grown in Africa. In overdose it is not pleasant.*

SURELY this is not an article on interplanetary hallucinogens or extraterrestrial aphrodesiacs. Nor is it a paper extolling the love-making enhancement of powdered rhinocerous horn, but it comes close. Yohimbine is a relatively new street drug whose origins are in Africa.

The Africa of my youth seemed to be a country of great mystery and intrigue; of European colonies, of wild animals and, of course, of Tarzan. Possibly my imagination was fueled by Edgar Rice Burroughs, Ernest Hemingway, Robert Ruark and the great movies like The Snows of Kilimanjaro, King Solomon's Mines, Stanley and Livingston, Bwana Devil, etc. Now the only thing about the country that is the same as I imagined it, is the shape — what with new countries with new names and new forms of government and famine and war and seemingly endless turmoil. But then again yohimbine comes from there. It was a gift we could have done without.

Yohimbine enjoys some reputation as an aphrodesiac and hallucinogen as advertised in pornographic magazines (my mother will not allow me to read them, so some of this material is hearsay) and also this drug is known to have stimulatory effects on the CNS. That's the good news. The bad news is that yohimbine is available by prescription and can be ordered in large quantities without prescription from mail order houses. It is available in some herb stores and can be brewed as a tea. I'm not sure why it has increased in popularity, but people who are "into drugs" seem to be constantly seeking new "highs" and "turn ons" and this one is being touted as a new "street" drug.

Yohimbine, believe it or not, is a drug that is found in the bark of yohimbe, which is an African tree. It is also listed in pharmacology texts as an *alpha-2 adrenoreceptor antagonist*. (You are joshing, aren't you, you want us to believe that African tree bark contains catecholamine inhibitors? The next thing you know you will have us believe that "sniffing" fire-extinguisher agent fumes can make us "high." Well actually, that is true, and may be the subject of a future anecdote.) Alpha receptors are present in the eye, blood vessels, genitourinary, and gastrointestinal tracts. The administration of alpha stimulating drugs such as norepinephrine or phenylpropanolamine or phenylephrine causes vasoconstriction, pupillary dilatation, a decrease in GI mobility and GI secretions, contraction of GI and GU sphincters and bladder contraction. So called "pure" alpha agonist poisoning could be predicted to cause hypertension and vagally mediated reflex bradycardia which could be life threatening. If you are ever faced with such an emergent situation, phentolamine (Regitine) is considered the antagonist of first choice. Alpha agonists can of course have powerful CNS effects such as tremor, seizures, panic reactions, sensory distortion, hallucinations and psychotic manifestations. If these latter clinical features are troublesome you could try diazepam (Valium) or haloperidol (Haldol) if the adrenergic antagonist fails.

Well, what about alpha-2 adrenoreceptor blockers, like yohimbine? These blockers (AKA antagonists) should produce, in overdose, miosis, postural hypotension, reflex tachycardia, angina (not common) and an increase in gastric acidity. The adrenergic blockers also have CNS effects, usually stimulation.

Alpha blocker poisoning is really not common. There are only a few types of these drugs around, e.g., phentolamine, phenoxybenzamine, prazosin, dibenamine, and of course, yohimbine. I mean really, pushers don't walk up to you on the street and say "Hey buddy, want to buy some phenoxybenzamine?" I have a cousin who tried to work his way through school (his ultimate ambition was to be a bartender at a rest camp for embattled secretaries of Department Chairmen) by selling Regitine as a street drug. Needless to say he failed and he is now confined to the Illinois State Home For The Criminally Foolish.

I suppose all of the above makes yohimbine's use as a drug of abuse really weird. The chemical known as yohimbine (AKA quebrachine, aphrodine, and corynine) is a *harmine* analog. Harmine and harmine-like chemicals have the potential to produce hallucinations. Harmine and harmatine are indole alkaloids found in several psychotropic plants, especially in the bark of certain South American vines. The alkaloids are hallucinogens and are rather powerful monamine oxidase inhibitors. Yohimbine (one street name is "Yo Yo") can produce an alpha adrenergic block of relatively short duration. Although CNS action does occur, it apparently is less than what occurs with ergot alkaloids. Although it has been recommended as a blood pressure lowering agent it can in fact *increase blood pres-*

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27104.

sure. Yohimbine can cause a local anesthetic action like cocaine as well as cause vasodilation of the skin and mucous membranes especially the sexual organs (please forgive me, I know this is a family magazine but I just couldn't help myself). It is currently being advertised as a smoking preparation whose ultimate purpose is "effortless seduction." (Land of Goshen, if one wants effortless seduction, one should make a visit to Madame CaCa's House of The Seven Moons on I-85.) This chemical can be ingested, smoked or imbibed as a tea.

Symptoms and signs of yohimbine overdose include weakness, hypertension, tachycardia and abdominal pain. Apparently massive overdose can produce generalized stimulation of the nervous system resulting in paralysis. It has been alleged that if this paralysis affects the intercostal muscles, the diaphragm, etc., then death can ensue simply because you stop breathing. Other adverse effects include irritability, tremors, antidiuresis and really a general picture of central excitation. Yohimbine enhances neural release of norepinephrine which may account for some of its sympathomimetic actions.

In a recently reported case of yohimbine overdose[1] as a result of drug abuse, the young victim experienced generalized weakness, paresthesias, loss of coordination and a dissociative state. This unhappiness was followed by chest pains, palpitations, tremors, severe headaches and dizziness. Upon examination at an emergency facility, she had hypertension, tachypnea, tachycardia, and temperature elevation. The patient was described as pale, tremulous and anxious. Her serum *norepinephrine* level was elevated. It is quite possible to identify yohimbine via high performance thin layer chromatography.

What should you do when confronted by such a patient, assuming you were able to make the diagnosis? (One solution is to call yourself on your pager and let someone else struggle with the case.) The management of yohimbine overdose can be very confusing. Although this drug is an alpha-adrenergic blocker and you would expect hypotension and reflex tachycardia as a result of overdose, we have seen that this drug can actually cause hypertension. It has been suggested, and quite appropriately in my opinion, that *clonidine* may be the drug of choice to reverse the adverse effects of yohimbine toxicity. Clonidine, you may recall, acts centrally by stimulating alpha-adrenergic receptors and causing a reduction in sympathetic tone as well as peripherally blocking alpha-adrenergic receptors and reducing vascular activity.

One of the aspects of seeing movies about Africa and reading stories about the "dark continent" is that we tend to forget that it was our first introduction to Swahili — the language of East Africa. The natives consistently referred to the employers as Bwana (sir, master, mister, boss, etc.). The other word you consistently heard at times of great excitement was Umgawa, Bwana!! (Remember?) Exhaustive research in the Swahili literature reveals no such word as umgawa. It probably was made up by Hollywood script writers. The main title of this treatise is in Swahili of course, and means "we have tried every medicine that you gave us but they are all useless." Now, doesn't that sound familiar — many the problems of the health care provider, no matter where in the world, they are universal. Jambo!!

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References

1. Linden CH, Rumack BH, et al. Yohimbine: A new street drug. Abstracts from the Proceedings of the AAPCC, AACT, ABMT, CAPCC Annual Scientific Meeting, San Diego, CA, October, 1984.

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INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg, for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

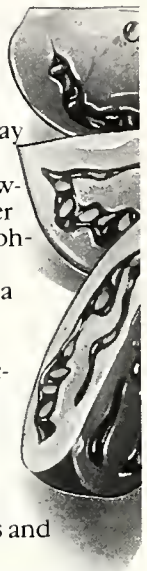
SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

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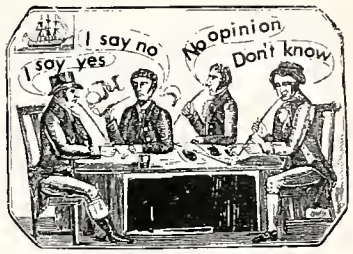


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Preadmission Certification: Does It Constitute the Practice of Medicine?



Eugene W. Linfors, M.D., editor

The question for April is: **In your personal opinion, does the refusal of precertification for admission to the hospital by insurance companies constitute the practice of medicine? Should they be held liable for malpractice?**

From Dr. J. Trig Brown, an internist in Durham.

It is well known that physicians are the major cause of escalating health care costs. To think that precertification for admission by insurance companies constitutes the practice of medicine is absurd; these benevolent companies are simply overseeing that area that physicians have failed so blatantly to police. The operating premise is that physicians use hospitals inappropriately for their own personal gains. Consider the following scenario.

MD: I'm calling for precertification for admission for my patient, Mr. N. Need.

Insurance Company (IC): What is the reason for admission?

MD: This elderly man has bad chronic obstructive pulmonary disease and is not doing well.

IC: Is not doing well . . . Doctor, what do you mean?

MD: Well, you see, his wife who performed his chest physiotherapy has just died, his fuel subsidy has been stopped, and he's now got an upper respiratory infection. I'm concerned that this may decompensate him.

IC: Nothing you have said allows me to authorize a hospitalization. What objective criteria do you have?

MD: On physical exam his respiratory rate is 30, he is somewhat febrile, and his sputum is green, thick, and tenacious.

IC: According to my guidelines a respiratory rate of 30 does not qualify for admission, what is his temperature?

MD: Orally it is 38^2; however, he has trouble keeping the thermometer in his mouth because of his dyspnea.

IC: 38^2 is not high enough, Doctor, you know we have our guidelines. Do you have blood gases?

MD: Why yes, his pO_2 is 58 and his pCO_2 is 52.

IC: Are those values acute onset, sudden onset, recent onset, or recently or newly discovered?

MD: What?

IC: *Acute* is within 6 hours, *sudden* is within 24 hours, *recent* is within one week, and *recently or newly discovered* was not present at the previous examination.

MD: Oh, I see. Well his gases at admission last fall were slightly worse, but we never repeated them because clinically he was doing so well until last week.

IC: So, these gases are not recently or newly discovered. Doctor, we are only trying to help you. What would you plan to do with the patient in the hospital?

MD: Mr. Need has always done well with twice daily percussion and postural drainage, adjustment of his theophylline, and antibiotics.

IC: Good, we're on to something. Will the theophylline and antibiotics be given intravenously?

MD: Well, no, actually we can get therapeutic levels orally at a cheaper cost and with less discomfort to the patient.

IC: Will he be on the intensive care unit?

MD: No, you see, Mr. Need has a living will and in it he stipulates that he not be on an intensive care unit.

IC: Well, Doctor, you have a problem. Although none of the objective information documents a severity of illness appropriate for admission, you do come close. But, on the other hand, the intensity of services planned do not substantiate the need for admission. I am sorry but I have no other choice but to disallow this request for hospitalization.

MD: I hear what you are saying but I still don't know how to adequately treat Mr. Need as an outpatient.

IC: I'm sorry Doctor, we don't practice medicine, that's your problem.

Physicians practice medicine and are liable for malpractice. The trend toward precertification for admission rekindles memories of Alexander Haig's infamous misstatement "I'm in charge here." It is clear the person in charge should be liable for malpractice and insurance companies are not in charge . . . or are they?

From Dr. Charles O. Boyette, a family practitioner from Belhaven.

In my opinion, preadmission certification requirements by insurance companies or any other designated body does indeed constitute the practice of medicine. Admission or denial of admission has a direct effect on how that patient is treated and managed, and in turn will significantly affect recovery from illness or continuing disability.

No physician is perfect and the practice of medicine is complicated and variable. It seems today that everyone — government, insurance carriers, and so many others — wishes to become involved and dictate how the sick are to be treated and under what circumstances. With these handicaps the ultimate loser will invariably be the patient. The attending physician and the patient will forever remain the most competent authorities as to the need for hospitalization.

As to liability in preadmission certification, there is no question but that insurance companies should be held liable in cases of denial for admission which results in disability or more severe consequences such as death. The prevention of a small number of admissions will never atone for the potential hazards and losses should the advice of the attending physician be ignored.

Doctors are being placed in an untenable and liable position and this should not be. Insurance companies and government are not practitioners of medicine. They should simply state what they can finance and what they can not in contracts with their clients and leave the practice of medicine to those who are professionals in patient care.

From Dr. William W. Fore, an endocrinologist in Greenville.

Most physicians consider the physician-patient contract for payment to be the responsibility of the patient and not his/her insurance company. Many physicians request payment of fees and then refund to the patient when the health insurance carrier pays. A denial in the precertification process is a declaration before the fact that the insurance carrier will not pay for the admission because their consultants believe the patient can be cared for as an outpatient. The patient's admission occurs from a decision that is made by the physician, the patient, and the hospital. It is not the practice of medicine for an insurance company to deny payment before the fact.

One industry in North Carolina obtained a 55% decrease in hospital utilization without having a patient denied by the precertification process. Precertification works and will be necessary unless all physicians in North Carolina work to voluntarily decrease hospital utilization.

From Clark C. Havighurst, a professor of law in Durham.

No. An insurer's refusal in advance to pay for a hospitalization advised by a physician does not constitute the practice of medicine. The insurer is not deciding on medical treatment but is only giving effect to a contractual limitation on its obligation to pay for marginally beneficial medical treatment. The patient is still free to decide, with his physician's advice, to accept hospitalization (at his own expense). The medical decision is thus entirely distinct from the insurer's decision on payment.

No. An insurer cannot be sued for medical malpractice. The insured's rights against the insurer are governed in the first instance by the insurance policy, and the proper claim in any lawsuit would be for breach of contract. Some states allow insureds to sue insurers for bad faith in interpreting policy language and refusing to pay valid claims, and punitive damages are occasionally awarded in such cases. Unless a court were thoroughly confused (they often are), the test for bad faith would not be anything like the test that would apply if a physician failed to provide the treatment in question. Moreover, because the insurer did not itself prevent treatment from being rendered, the damages would probably not be measured by the injury suffered.

From Dr. Andrew W. Walker, a plastic surgeon in Charlotte.

No, I do not believe the refusal of precertification for admission to the hospital by the insurance companies constitutes the practice of medicine. The physician has a responsibility to recommend to his patient whether he or she should be admitted to the hospital. The insurance company decides whether the hospital and the physician should be paid or not. This in no way should interfere with what the doctor feels is right for his patient. The patient and insurance company have entered into an agreement without the doctor's input. The patient must, therefore, bear the burden of the bill if the insurance company elects not to pay it. The physician should remind the patient that this is the case. A second opinion could be gotten from a second physician if the patient so wishes. I believe if the insurance company has refused too many patients for hospitalization they may be sued by their clients and the courts would then have to decide if it was a failure to fulfill a contract. Whether this would constitute malpractice or not I do not know.

• EDITOR'S NOTE: Two of our respondents argue that refusal of precertification for hospitalization does constitute the practice of medicine while three see it as a separate contractual issue between the insurance company and the patient. Informal discussions with some of my colleagues have mirrored this difference of opinion. I don't think we've heard the end of this discussion.

Five opinions, even when stated as well as our respondents have, do not constitute a true survey. I try to anticipate several sides to an argument in asking for opinions. I am grateful to those who do respond. Some, for various reasons, choose not to respond in print. If, after reading the Forum, you see a particular point of view underrepresented, please write it down and send it to me.

We also invite opinions on the question for the next Forum. **"What would you advise our Medical Society to do and say regarding ecology and pollution?"** Please send your response by April 22 to: Eugene W. Linfors, M.D., Box 3381 Duke University Medical Center, Durham 27710.

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C.* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068

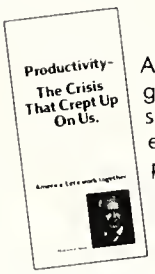
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Coalition on Sexually Transmitted Diseases

Marguerite K. Tracy

EDITOR'S NOTE: *A coalition* to combat sexually transmitted diseases has been formed by the United Way of Charlotte. They hope that the Coordinating Council of Specialty Societies will submit a report which will be presented to the House of Delegates at the annual meeting of the North Carolina Medical Society. The exact wording of such a report has not been finalized, but the gist can be summarized by three resolutions. These resolutions were formulated because the members of the Coalition believe that there is a need for private patients to have an alternative to public health clinics and access to a fee-for-service physician, knowledgeable in both the diagnosing and treating of sexually transmitted diseases. The Coalition believes that there is a large pool of physicians in North Carolina capable of treating sexually transmitted diseases, but there is no readily identifiable mechanism whereby private patients can be referred to fee-for-service physicians. The three resolutions follow:*

RESOLVED, that the North Carolina Medical Society commit itself to a public service project for the people of North Carolina by organizing a statewide network of physicians who would be willing to accept referral of private *"Fee For Service" patients for the evaluation and treatment of sexually transmitted diseases; and BE IT FURTHER*

RESOLVED, that the North Carolina Medical Society, in cooperation with AHEC and other educational resources, would provide continued medical education in sexually transmitted diseases for those physicians who join in this statewide network of private physicians; and BE IT FURTHER

RESOLVED, that the North Carolina Medical Society, after creating the network, commit itself to a public awareness program, and facilitate the general public's accessibility to this statewide physicians network.

The following article contains the background information that led to the formation of the Coalition.

** Further information about the Coalition can be obtained from Pete Auerbach at 704/375-0222. Mrs. Marguerite Tracy of Charlotte, chairman of the Coalition, is immediate past president of the North Carolina Medical Society Auxiliary. The current members of the Coalition are Melinda Wharton, M.D., Durham; Don C. Chaplin, M.D., Burlington; Albert M. Collier, M.D., Chapel Hill; Robert Greenup, Fort Bragg; Dr. Raphael DiNapoli, Raleigh; Raymond S. Combs, Camp Lejeune; Robert Williams, M.D., Seymour Johnson AFB; James Fowler, Jr., Raleigh; Frankie Barnes, Raleigh; June Stallings, Raleigh; George Shackelford, Raleigh; Martha Jacob, Jacksonville; Lottie Daw, New Bern; Pam Kohl, Raleigh; Gwin Hughes, Raleigh; Lorey White, Jr., Louisburg; Frank McFall, Atlanta, GA; Margie Rose, Raleigh; Family Life Council of NC, Raleigh; Kate Garner, Ph.D., Greensboro; Hugh Tilson, M.D., Research Triangle Park; Roy Parker, Jr., Fayetteville; Charles Russell, Wilson; Spurgeon Cameron, Raleigh; Fred Sparling, M.D., Chapel Hill; Sandra Mayben, Fayetteville; Harry A. Gallis, M.D., Durham; Nick Engel, Winston-Salem; Brenda S. Coble, R.N., Greensboro; Midgie Rawley, Charlotte; Dean Garver, Shelby; Madeline Hunter, Winston-Salem; Lauren Kirkpatrick, Raleigh; David Citron, M.D., Charlotte; Kathryn M. Frye, Charlotte; A. D. Sawyer, Chapel Hill; Pete Auerbach, Charlotte.*

The problem

Back in the 1940s, we assumed that antibiotics would forever control the terrible diseases such as tuberculosis and syphilis, which were at that time common and pandemic. For the next 20 years health care personnel became very complacent as they saw the "wonder drugs" cure these ills and others.

During this period of complacency, a new pandemic of sexually transmitted diseases has developed. In spite of wonder drugs, we are back to the drawing board. Some of

the newly identified sexually transmitted diseases have probably existed for centuries. Improved laboratory and epidemiologic investigations have defined the extent of the epidemic and the life-threatening consequences of these diseases. The "coming of age" of the children of the post-World War II baby boom has made the control of sexually transmitted diseases more urgent. There are simply more people and more sexual activity.

We now recognize not only two sexually transmitted diseases but 26, including herpes, hepatitis, and AIDS. And yet only two diseases are required to be reported: gonorrhea and syphilis.

The National Institute of Allergies and Infectious Diseases Study Group reported that in 1980, the incidence and occurrence of sexually transmitted diseases were as follows:

- 7 million new or recurrent episodes of genital herpes
- 3 million infections due to chlamydia
- 3 million trichomoniasis cases
- 2 million cases of gonorrhea
- 0.5 million cases of venereal warts, and
- 0.1 million new cases of syphilis

These millions of cases in turn led to:

- 1 million cases of pelvic inflammatory disease
- 0.3 million damaged infants
- 0.2 million women rendered infertile, and
- *$2.5 billion* in direct and indirect costs.

They also cause death, physical deformity, mental retardation, ectopic pregnancy, infant pneumonia, and possibly five different cancers.

These numbers are misleading because they represent only a fraction of actual cases. Venereologists estimate that these numbers may represent only 1/10 of all cases. Most of the reported cases are hospital or clinic based. A study performed by the American Social Health Association in 1963 and 1971 revealed that no more than 12% of sexually transmitted diseases treated by U.S. physicians were reported. A 1980 *American Journal of Public Health* article reported that approximately 60% of gonorrhea cases seen by private physicians in Denver, Colorado, were not reported.

Many persons who are carrying some sexually transmitted diseases have no symptoms. Consequently, there is much unrecognized spread of diseases like chlamydia, gonorrhea, and especially herpes.

Let's look at some specific diseases and their influence.

Gonorrhea. Although more than 1 million cases have been reported in the U.S. annually for the past four years, it is believed there are over 2 million actual cases per year. The highest rates of infection are found among young adults, ages 20 to 24 years, and teenagers, ages 15 to 19. An estimated one of every 30 teens in the 15 to 19 age group will contract gonorrhea each year. Women continue to be the primary victims of gonorrhea, accounting for 90% of all complications.

Chlamydia. Results of studies indicate chlamydia has overtaken gonorrhea as the number one sexually transmitted disease. Since chlamydia is difficult to recognize by the female patient and difficult to culture, and because reporting is not mandatory, documentation of prevalence is difficult. But, again, women are the major victims of the disease, which is responsible for at least 20% of all pelvic inflammatory disease, 11,000 cases of sterility, and 3600 ectopic pregnancies.

Syphilis. According to the Centers for Disease Control in Atlanta, reports show that within the last two years there has been a surge in the number of cases of syphilis, to approximately 100,000 new cases each year.

Herpes. This was first identified in 100 A.D. It now affects 15 to 20 million Americans representing 500,000 new cases annually. Women and children are the primary victims. Because of ineffective control and an average annual recurrence rate of 5%, this disease is expected to rise rapidly. There is no cure for herpes.

Acquired Immuno-Deficiency Syndrome (AIDS). More than 40% of those infected are dead within a year; there is no cure. Since 1981, AIDS has struck 788 people in the U.S. and 57 abroad, killing 295. What a waste to us individually and collectively!!

North Carolina had the first venereal disease control program in the U.S. in the early 1930s. This was a program paid for by Z. Smith Reynolds Foundation, which is still interested and involved.

Some startling facts are:

- North Carolina has the 7th highest rate of gonorrhea in the nation.
- North Carolina ranks tenth in the nation in the amount of syphilis. Charlotte has a reported infectious syphilis rate nearly seven times the national average.
- In 1983, 425 children between the ages of 10 and 14 years were reported to have been infected with gonorrhea in the past year. A total of 1123 young people between the ages of 15 and 19 years were infected in North Carolina in 1983.
- Currently, there are 2 million cases of gonorrhea annually identified, costing about $1 billion annually!
- Reported cases of syphilis have doubled annually since 1961.
- Over 80 cases of AIDS have been reported and verified in North Carolina.
- The most startling fact: *one of every four individuals in the work place is infected by a sexually transmitted disease* (this is a report from the Public Health Disease Center in Atlanta).

With all this, we do not calculate the cost in dollars suffered by industry because of related illness, absenteeism and poor performance on the job.

Our Solution

We do know what we should do to set up a control program. The Coalition on Sexually Transmitted Diseases is composed not only of health care personnel, such as doctors, public health nurses, and members of the State Infectious Disease Programs, but also includes industry, the military, social services, the North Carolina Medical Society, the North Carolina Medical Society Auxiliary, the state PTA, youth advocacy personnel, the Department of Public Education and others.

The Coalition has drafted five goals and related

strategies for reducing this pandemic. Our first objective is *to insure that every student in North Carolina receives accurate, timely education about sexually transmitted diseases as part of a comprehensive health education curriculum.* Because of a policy statement sent to and passed by the legislators in June 1984, 16 additional health coordinators were added. We now have 32 health education coordinators.

The second objective is *to improve the public's understanding of sexual transmitted diseases, and their social and economic impacts, as well as its knowledge of preventive techniques and treatment options.* The Coalition purposes to accomplish this through a public awareness program, using appropriate levels of information. Much of present material is out-dated, obsolete, and inconclusive.

The third objective is aimed at *developing training programs for health professionals to accord them current information.* This can be accomplished by providing the health education and clinical experience in schools for health professionals.

The fourth objective will *encourage every employer (industry, military, commerce and government) to provide health services at the work place to include sexually transmitted disease education, testing and health care.*

The fifth objective deals with *improving and increasing access to services in the treatment of any sexually transmitted disease.* This will include evaluation of hours of operations of clinics, to be more compatible with patient needs and to more involve qualified physicians to provide answers, care and treatment.

The Coalition is composed of quality people with a caring concern for the community and it is their hope to provide a better understanding and an increased awareness of this major health problem.

This is but a portion of the program of work, but is a good synopsis of the direction of the Coalition.

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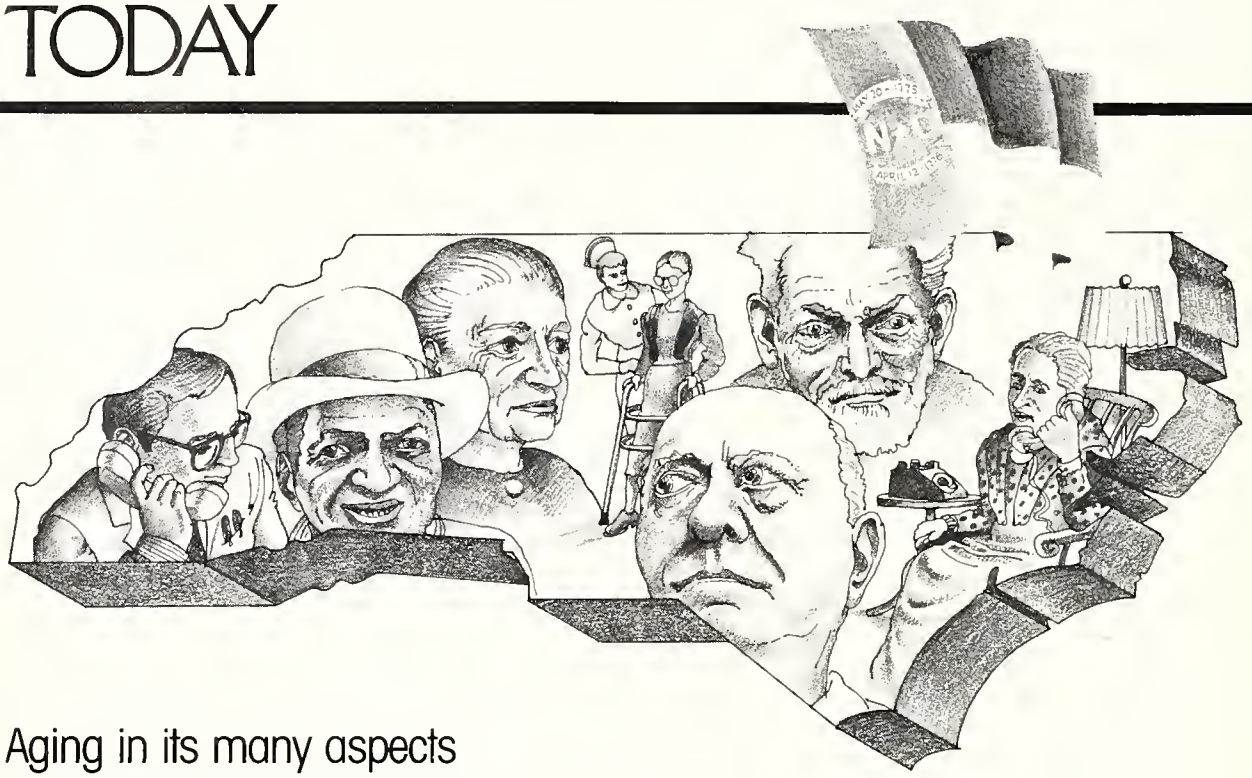
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NORTH CAROLINA MEDICINE TODAY



Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

References: **1.** Hasan MK, Slack NL, Mooney RP. *W Va Med J 79* 98-102, May 1983. **2.** Manton KG, Woodbury MA. *J Gerontol 38*.406-413, Apr 1983. **3.** Siegler IC, McCarty SM, Logue PE. *J Gerontol 37*.176-181, Feb 1982. **4.** Hess TM, Higgins JN. *J Gerontol 38* 65-71, Jan 1983. **5.** Roach M. *NY Times Mag*, Jan 16, 1983, p. 22. **6.** Gwyther L. *NC Med J 44* 434-436, Jul 1983

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*Feighner JP, *et al Psychopharmacology* 61:217-225, Mar 22, 1979.

Please see summary of product information on following page.

LIMBITROL® Ⓥ Tranquilizer-Antidepressant
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and blooting. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric. Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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Annual Meeting Program

131st Annual Meeting of the North Carolina Medical Society, May 1-5, Pinehurst Hotel, Pinehurst, NC.

Wednesday, May 1

9:00 a.m. Resident Physician Section, *Crystal Room*
1:00 p.m. Resident Physician Lunch, *Main Dining Room, West End*
2:00 p.m. Medical Mutual Insurance Company Risk Management Seminar, *Cardinal Ballroom*
Committee on Blue Shield, *Pine Room*
2:15 p.m. Resident Physician Section, *Crystal Room*
6:30 p.m. Resident Physician Reception, *West Porch*
7:00 p.m. Resident Physician Dinner, *Crystal Room*

Thursday, May 2

7:00 a.m. AMA Delegation Breakfast, *Crystal Room*
8:00 a.m. MEDPAC Board, *Pine Room*
8:30 a.m. Section on Public Health and Education, *Azalea Bar*
10:00 a.m. House of Delegates, *Cardinal Ballroom*
11:45 a.m. Lunch Buffet, *Main Dining Room*
12:00 p.m. MEDPAC Lunch, *West Lawn*
2:00 p.m. Reference Committee I, *Cardinal Ballroom*
Reference Committee II, *Azalea Bar*
Reference Committee III, *Board Room*
Section on Otolaryngology and Maxillofacial Surgery, *Crystal Room*
Section on Urology, *Pine Room*
6:00 p.m. ECU School of Medicine Alumni Reception, *West Porch*
Medical College of Virginia Alumni Reception, *Lower Lobby*
Exhibitors' Reception, *West Lawn*

Friday, May 3

7:00 a.m. NCMS Officials Breakfast Caucus, *Main Dining Room*
8:30 a.m. Conjoint Session, *Cardinal Ballroom*
N.C. Academy of Family Practice, *Azalea Bar*
N.C. Pediatric Society Executive Committee, *Room 129*
9:00 a.m. First General Session, *Cardinal Ballroom*
Section on General Surgery and Section on Plastic and Reconstructive Surgery, *Resort Club*
Obstetrics/Gynecology Liaison Committee, *Mid Pines Resort*
9:30 a.m. N.C. Commission for Health Services, *Pine Room*
10:00 a.m. N.C. Pediatric Society Liaison Committee, *Crystal Room*
11:00 a.m. N.C. Orthopaedic Association Executive Committee, *Magnolia Room*
11:45 a.m. Lunch Buffet, *Main Dining Room*
12:00 p.m. N.C. Academy of Family Physicians Lunch, *Main Dining Room, West End*
Section on Ophthalmology Lunch, *Main Dining Room, East End*
N.C. Orthopaedic Association Executive Committee Lunch, *Magnolia Room*
12:30 p.m. N.C. Pediatric Society Liaison Committee Lunch, *Crystal Room*
1:00 p.m. N.C. Orthopaedic Association, *Pine Room*
2:00 p.m. Section on Pediatrics and Section on Allergy and Clinical Immunology, *Cardinal Ballroom*
Section on Ophthalmology, *Crystal Room*
Section on Orthopaedics, *Pine Room*
Section on Family Practice, *Azalea Bar*
Section on Emergency Medicine, *Magnolia Room*
Medical Student Section, *Room 129*
N.C. Society of Internal Medicine Executive Committee, *Merion Villa*
Section on Obstetrics and Gynecology, *Mid Pines Resort*
Section on Plastic and Reconstructive Surgery Business Meeting, *Mid Pines Resort*
5:00 p.m. Section on Allergy and Clinical Immunology Business Meeting, *Board Room*
N.C. Society of Internal Medicine Reception, *Merion Villa*
5:30 p.m. Duke University Medical School Alumni Reception, *Front Porch West End*
UNC School of Medicine Alumni Reception, *West Porch*
6:00 p.m. Bowman Gray School of Medicine Alumni Reception, *Azalea Bar Porch*
6:30 p.m. President's Reception, *Lower Lobby*
7:30 p.m. President's Dinner and Dance, *Cardinal Ballroom*

Saturday, May 4

7:00 a.m. NCMS Officials Breakfast Caucus, *Main Dining Room*

8:00 a.m. Section on Dermatology, *Crystal Room*
Section on Anesthesiology, *Pine Room*
Section on Neurology and Section on Psychiatry, *Azalea Bar*

8:30 a.m. Second General Session/Section on Internal Medicine, *Cardinal Ballroom*

9:00 a.m. Section on Radiology and Section on Nuclear Medicine, *Magnolia Room*
Section on Pathology, *Resort Club*

10:00 a.m. Committee on Mediation, *Board Room*

11:30 a.m. Section on Psychiatry Business Meeting, *Azalea Bar*
Section on Neurology Business Meeting, *Room 129*

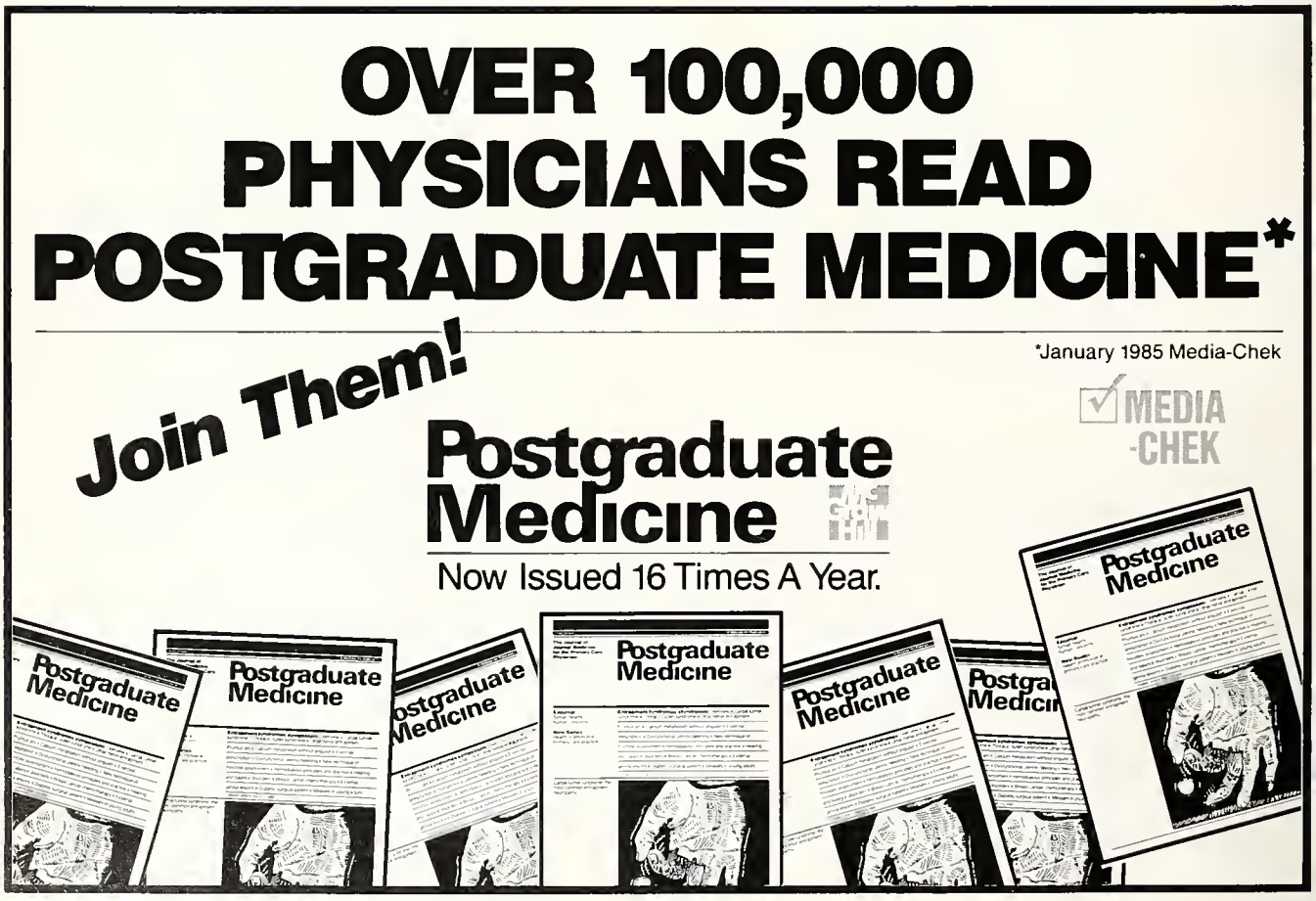
11:45 a.m. Lunch Buffet, *Main Dining Room*

12:00 p.m. Section on Dermatology Lunch, *West Porch*
New Hanover-Pender Lunch and Caucus, *Board Room*

12:30 p.m. Pitt County Caucus, *Room* 129

1:00 p.m. Mecklenburg County Caucus, *Azalea Bar*
Forsyth County Caucus, *Magnolia Room*

2:00 p.m. House of Delegates, *Cardinal Ballroom*
Section on Neurological Surgery, *Crystal Room*




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NORLESTRIN®
(1 mg norethindrone
acetate and 50 mcg ethinyl
estradiol tablets)
USP 1/50
BECAUSE SOMETIMES A 50 IS PREFERABLE.

Brief Summary of Prescribing Information
NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information. A Brief Summary follows.

DESCRIPTION
Norlestrin Products are progestogen-estrogen combinations

INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years; in clinical trials with Norlestrin 2.5/50 involving 96,388 cycles, there was a pregnancy rate of 0.22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See WARNING No. 5)
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved.

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema, or retinal vascular lesions.

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy. Birth Defects in Offspring, and Malignancy in Female Offspring.* During early pregnancy female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who continue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected. (a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema; chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine; increase in size of uterine leiomyomata, rash (allergic); mental depression; reduced tolerance to carbohydrates, vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome; cataracts; changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis, porphyria.

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Norlestrin [21] 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [21] 2.5/50 is available in compacts each containing 21 tablets. Each tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [Fe] 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [FE] 2.5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [28] 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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The Diagnosis of Viral Pneumonitis in a Compromised Host: Is An Aggressive Approach Warranted?

Dale Sargent, M.D., Elizabeth Mease, M.D., and James F. Howard, Jr., M.D.

• *Transbronchial biopsy was necessary to find the cause of illness in a woman immunocompromised by treatment for her myasthenia gravis.*

WHEN evaluating a pulmonary infiltrate in an immunocompromised host, one is faced with an endless array of possible causes for these infiltrates, both infectious and non-infectious. Empiric therapy directed at even a few of the most likely pathogens involves regimens with serious potential for toxicity. An aggressive diagnostic approach in these patients will often allow more specific and less toxic therapy resulting in an overall decrease in morbidity. The following case illustrates this principle.

A 60-year-old woman had myasthenia gravis for 18 months. Her treatment consisted of cholinesterase inhibitors; intermittent plasma exchange; a prior thymectomy; azathioprine, 50 mg three times daily; and prednisone, 70 mg every other day. She presented with three weeks of fever; night sweats; anorexia; weight loss; and painful, migrating, red skin papules. For two weeks, she had a non-productive cough without hemoptysis or chest pain.

Physical exam revealed a cushingoid, tachypneic woman with a temperature of 37.8°C. There were red, non-fluctuant, 1-2 cm tender papules on the right arm, buttocks, and left anterior tibial region. There were findings of consolidation over the left upper lobe of the lung and +2 pretibial edema. She had 4/5 muscular strength. The white blood cell count was 8,800/mm^3 with a normal differential. A chest radiograph showed an alveolar infiltrate in the left upper lobe (figure 1).

Multiple blood, urine, and sputum cultures were negative for bacterial pathogens, fungi, and mycobacteria. A skin biopsy of the papules showed acute and chronic inflammation with no pathogens seen on histologic sections or culture.

Although the patient seemed to have an infectious illness, the differential diagnosis was broad. Because of the length of her illness, we felt routine bacterial pathogens were unlikely. More likely were the opportunistic pathogens such as pneumocystis (although it rarely causes focal infiltrates), fungi (including blastomyces, aspergilli, and cryptococci), tuberculosis, legionella, or nocardia. The viral pneumonias seemed unlikely, again because of the focality of the infiltrate. Clearly it was impossible to initiate therapy for all of these organisms, so a diagnostic procedure was performed.

In our hands, transbronchoscopic lung biopsy is diagnostic in over 75 percent of compromised hosts with pulmonary infiltrates. The morbidity and mortality of this procedure are also very low. Therefore, on Day 2, a transbronchial biopsy was done. The biopsy showed a polymorphonuclear infiltrate, interspersed with lymphocytes and plasma cells. Intranuclear inclusions, consistent with cytomegalovirus (CMV), were present (figure 2). Stains and cultures for bacteria, legionella, mycobacteria, and fungi were negative.

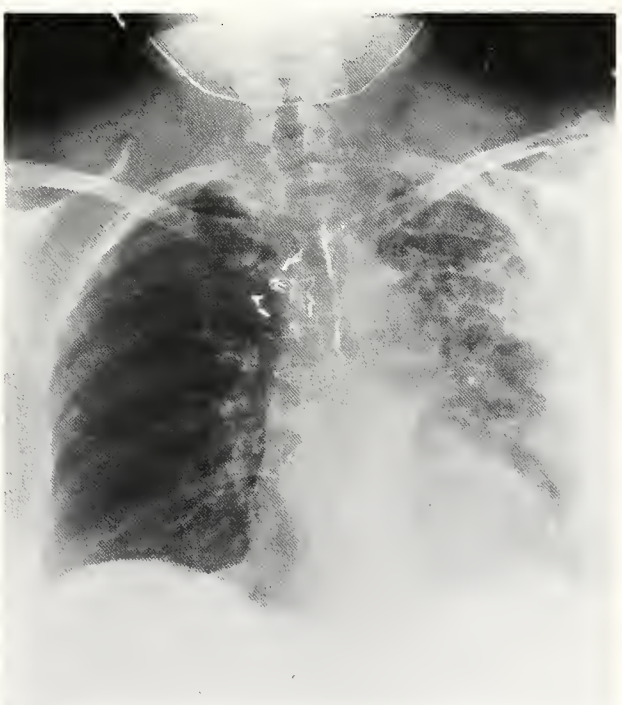


Figure 1. *A chest radiograph on hospital Day 10 showing the left upper lobe alveolar infiltrate.*

From the Division of Pulmonary Diseases, Department of Medicine and Department of Neurology, University of North Carolina School of Medicine, Chapel Hill 27514.

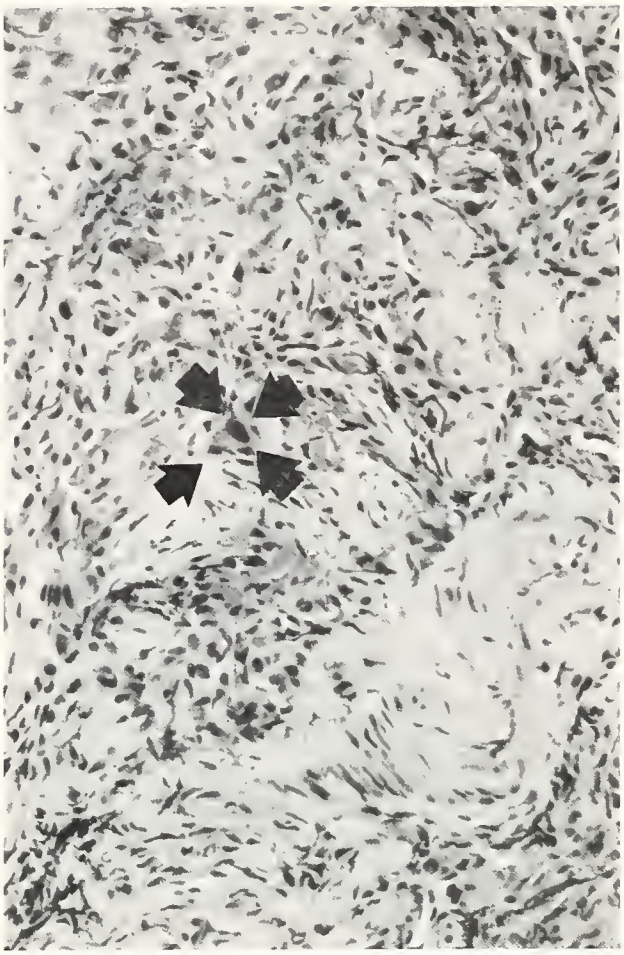


Figure 2. *A section from the transbronchial biopsy showing an intranuclear inclusion (arrows) consistent with CMV infection (hematoxylin and eosin, original magnification × 250).*

Despite the finding of CMV on the initial biopsy, we were unwilling to ascribe the illness to CMV alone. CMV has been described to cause focal infiltrates only rarely[1, 2] and CMV infection frequently occurs in the company of other pathogens[1, 3] (table 1). Therefore, we began Amphotericin B, Isoniazid, and Rifampin; stopped her azathioprine; and decreased her prednisone to 40 mg every other day. She continued to do poorly, with progression of her pulmonary infiltrates and continued fevers. Vancomycin was added on Day 6 and Trimethoprim/Sulfamethoxazole, on Day 10.

Because we were still worried that a significant pathogen was present and had not been diagnosed, we repeated the transbronchial biopsy on Day 11. The findings were similar to the previous biopsy, including the presence of intranuclear inclusions. Cultures of the specimen grew CMV but no other pathogens.

With this additional information we felt comfortable with the diagnosis of CMV pneumonia. All antimicrobial agents were stopped and her subsequent course was marked by gradual return of her temperature to normal and clearing of her infiltrate. Complement fixation titers to antibody to CMV were 1:256 both "acutely" and after recovery. She was discharged on Day 23 and remains well nineteen months later, taking only prednisone as an immunosuppressant.

Table 1
Pathogens Frequently Associated with CMV in the Lung

Pneumocystis Carinii
Herpes Simplex
Candida and Other Fungi
Gram Negative Bacilli

The diagnosis of CMV pneumonia was established by culture and pathologic examination of lung tissue. Although lobar CMV pneumonia is exceedingly rare, exhaustive investigation did not reveal other agents. Furthermore, our patient received inadequate therapy for fungal, mycobacterial, or pneumocystis pneumonia and did not begin to improve until all antimicrobials were stopped. The failure of CMV titres to rise does not exclude CMV disease, since the initial titres were drawn three weeks into the illness. Also, CMV titres may fail to rise in compromised patients with the most severe CMV disease.[1] The nodular skin lesions have been described as a manifestation of CMV disease and may represent cutaneous CMV infection.[4]

Outside of the transplant and acquired immunodeficiency literature, there are scant reports of CMV pneumonia.[1, 3-7] Both our patient and those reported by Dowling[5] were receiving cytotoxic therapy in addition to corticosteroids, suggesting an additive effect between these classes of drugs with respect to CMV disease.

Confirmation of the diagnosis of CMV pneumonia allowed us to stop several toxic antimicrobial agents. The importance of tapering or stopping her immunosuppressive therapy was emphasized and, we believe, led to this patient's recovery. In immunocompromised patients with pulmonary infiltrates, an aggressive diagnostic approach is indicated. If routine examination and culture of clinical specimens are not revealing, we believe either transbronchial or open lung biopsy is indicated, depending on the level of expertise available at a particular institution. Viral cultures should be obtained on biopsy specimens, even if the clinical picture does not seem to indicate viral infection. The isolation of CMV as the pathogen from a lung biopsy may allow the patient to be treated without potentially toxic antimicrobials even though specific therapy for CMV is not presently available.

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Transdermal Nitroglycerin

Lisa Hutchinson, Pharm.D.

IN 1982, three nitroglycerin products utilizing transdermal drug delivery systems entered the U.S. marketplace. These products were conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease pending final approval after clinical trials were completed. Until this time, the cutaneous application of nitroglycerin ointment was the only method available (except high dose oral isosorbide dinitrate) which avoided a high degree of inactivation in the liver. The ointment, although used successfully in the treatment of angina pectoris and congestive heart failure, had several limitations. It was inconvenient for many patients to have to apply an ointment several times daily, especially when it had to be covered with an occlusive dressing. The amount of drug absorbed varies with the area of skin over which it is spread, the ointment thickness, and the intrinsic properties of the skin at the application site.[1] The ointment is rather messy and not very practical for active patients. The innovation of the transdermal patches was intended to overcome these problems.

The purpose of this article is to review the pharmacology, pharmacokinetics, efficacy and use of the three transdermal nitroglycerin products currently available in the United States.

Pharmacological Properties

Angina pectoris occurs when there is an imbalance between oxygen supply and demand to the myocardium.[2, 3] The determinants of myocardial oxygen consumption are: 1) tension development during myocardial systole, 2) the contractile state of the heart and 3) the heart rate.[2] Symptoms of ischemia occur when the demand for oxygen by the myocardium cannot be met by the coronary blood flow.[2, 3] This is usually the result of coronary atherosclerosis which causes blockage of the coronary arteries, decreasing the blood supply to the myocardium.[2, 3] The area of the myocardium supplied by the blocked arteries becomes ischemic as the difference between supply and demand increases.[2, 3] This is usually accompanied by angina pain.[2]

Nitrates relieve angina pain by improving the balance between myocardial oxygen demand and supply.[2, 3] All nitrates act by causing smooth muscle relaxation which produces dilatation of arteries and veins.[2, 3] Although the exact mechanism of nitrate action at the cellular level is not completely understood, it has been proposed that nitroglycerin acts by combining with sulfhydryl groups on nitrate receptors in vascular smooth muscle.[4] Ignarro et al also suggest that vasodilation results when cellular cyclic GMP is increased by nitrate induced S-nitrosothiol production.[5] Dilatation of the venous system results in pooling of the blood in the peripheral veins, leading to a reduction in right heart blood return, cardiac filling (preload) and decreased tension on the walls of the heart.[2, 3] The lowering of systemic vascular resistance when the arterioles dilate produces a decrease in pressure against which the left ventricle must pump (afterload).[2, 3] Decreased mechanical activity, therefore, lowers myocardial oxygen requirements and metabolism.[2, 3]

Nitroglycerin's effect on the coronary arteries is less well understood. It has been shown to dilate normal and diseased coronary arteries and to increase blood flow to coronary collateral vessels.[6-8] During ischemia, nitroglycerin increases flow to the subendocardium, re-establishing the normal 1:1 relationship of endocardial and epicardial blood flow, thus increasing blood flow to ischemic zones of myocardium.[9]

In summary, nitroglycerin may relieve ischemia by decreasing myocardial oxygen demands and left ventricular diastolic pressure; by reversing coronary vasospasms; by decreasing coronary arteriolar resistance; and by improving regional blood flow. For a more in-depth discussion of the pharmacologic properties of nitroglycerin the reader is referred elsewhere.[3-9]

Clinical Trials

Numerous studies have been done to evaluate the utility and therapeutic efficacy of nitroglycerin patches.[10-17] The data documenting the antianginal effects of nitroglycerin patches and the comparative magnitudes and duration of this activity differ between studies.

Thompson studied eight patients in a double-blind crossover study comparing Nitro-Disc to placebo.[10] All patients were men, ages 38-70, with class II or III angina, coronary heart disease documented by coronary angiography or previous documented myocardial infarction, and characteristic ST-T segment changes during exercise; they were receiving no other medications. The patients were titrated over a 10 day period to receive the appropriate dose of nitroglycerin. This was done by starting with a 16 mg patch and increasing by one patch per day until persistent headache occurred or other side effects precluded further increase. The daily dose was then adjusted to that insufficient to produce side effects. All patients underwent treadmill exercise tests according to the Bruce protocol. The test involved four stages: a baseline exercise test on day 1, exercise tests 2 and 26 hours after receiving a placebo or nitroglycerin patch on days 12 and 13, exercise tests 2 and 26 hours after receiving the opposite treatment on days 15 and 16 and a follow-up exercise test on day 19 to establish baseline stability. They concluded that the Nitro-Disc in-

creased the mean exercise capacity by 30% ($p < 0.05$) and that 26 hours after application the mean exercise duration was still prolonged by 25% ($p < 0.05$).

Reichek et al studied fourteen subjects (13 men and 1 woman) aged 50-70 with typical angina using a randomized double-blind placebo evaluation.[11] Coronary artery disease was documented by coronary angiography, exercise thallium or exercise echocardiographic studies. Eleven subjects received beta-blockers and five received calcium antagonists at a fixed dose throughout the study. Exercise testing was done on a Godart bicycle using the protocol of the National Institutes of Health. Seven subjects received a titrated low dose protocol, which is the smallest dose that would lower the cuff systolic pressure by 10 mm Hg or increase the heart rate at least 10 beats per minute in less than 2 hours. All received a baseline exercise test, then exercise tests after 4, 8 and 24 hours for 4 days during which they received either nitroglycerin patch or placebo. The effect of each subject's usual dose of sublingual nitroglycerin as a positive control was assessed on day 5. They concluded that there was no enhancement of exercise tolerance at 4, 8 or 24 hours after administration of the patch. A high dose protocol was then initiated using a maximal tolerated dose, defined as the dose that decreased systolic pressure to 90 mm Hg in normotensive, sitting patients or the largest dose that did not produce intolerable headaches. Improved exercise tolerance was seen at 4 and 8 hours, but was not seen at 24 hours. Even at maximal doses they found the effect on exercise tolerance to be surprisingly small. They suggest that nitroglycerin patches do not offer 24-hour coverage and would not recommend their antianginal effects to last for more than 8 hours.

The short- and long-term effects of various Nitro-Dur formulations on performance and hemodynamics were studied by Hollenberg.[12] A treadmill exercise test according to the Bruce protocol was used during this single-blind, dose-titrated study of 15 men with stable angina with positive treadmill exercise tests. After a control exercise test, each subject was tested at 4 and 7 hours with each of three different doses of Nitro-Dur (5 cm^2, 10 cm^2 and then either a 15 cm^2 or 20 cm^2 patch). After these short-term tests, long-term tests were begun. These tests were conducted on the first day of the study, both 2 weeks and 4 weeks after daily therapy was started, and 1 week after the application of a placebo patch. Results were that Nitro-Dur improved exercise tolerance by 31% ($p < 0.0001$) and the time required for 1 mm ST segment depression increased by 33% ($p < 0.0001$) in the short-term tests at all dosage levels. The long-term tests showed that the effects of Nitro-Dur on blood pressure became attenuated at 2 and 4 weeks, but cardiac responsiveness was preserved. They suggest drug tolerance or a neural-hormonal compensatory response to prolonged nitrates as the mechanism.

Georgopoulous et al studied the effects of the nitroglycerin patch in a randomized double-blind cross-over study.[13] A 25 mg nitroglycerin patch or a placebo patch was applied to 13 male patients, aged 32-63, with chronic, stable angina for 2 weeks and then the opposite treatment was applied for another 2 weeks. Exercise tolerance according to the Bruce protocol was performed at baseline and every week. Severity and duration of anginal pain evoked by exercise was recorded, and the intensity of the symptoms was graded on a four-point scale. ST-segment depression was measured according to Goldman. They found that transdermal nitroglycerin reduced the daily frequency of anginal attacks by 67%, the daily consumption of nitrates by 63% and exercise induced ST-segment depression by 50%. The anti-anginal effect was found to be more pronounced in the second week of treatment.

In a randomized double-blind, double cross-over trial of four one-week periods, Crean et al studied the effects of 25 mg of nitroglycerin in a 10 cm^2 patch versus placebo in 10 patients with stable angina and significant coronary disease.[14] Efficacy was assessed weekly by anginal diaries, exercise testing and 96 hours of ambulatory ST-segment recordings. They found that the nitroglycerin patch did not significantly reduce the number of anginal attacks per week, the consumption of sublingual nitroglycerin, the time to ST-segment depression, or the time to angina from that of the placebo patch. They concluded that no significant differences could be detected in objective or subjective signs of ischemia in patients treated with transdermal nitroglycerin or placebo.

There have been numerous investigations of the efficacy of nitroglycerin patches in the treatment of chronic stable angina. These studies differ significantly in their criteria for entry and efficacy, as well as in the use of concomitant medications and in the doses of nitroglycerin patch form supplied. The studies also use very small patient populations, therefore making the statistical significance of their conclusions difficult to interpret. It would be advantageous to develop a standard protocol in order to evaluate the efficacy of the patches. Studies that have the most effective design are double-blind, double cross-over, randomized placebo-controlled studies that try to maximize the amount of nitroglycerin applied. Until more standard protocols with larger patient populations are used, it will be virtually impossible to interpret these studies appropriately.

Pharmacokinetics

Transdermal drug delivery allows the drug to be absorbed from the skin into the capillaries under the skin and into the general circulation. This avoids the variable absorption sometimes associated with oral therapy and maintains a relatively constant drug level in the blood.[18] Transdermal drug delivery results in release of nitroglycerin at a rate that mimics a constant intravenous infusion.[19]

Although it is possible to measure plasma concentrations of nitroglycerin, there is no real correlation between plasma concentrations and pharmacological effects.[20, 21] Differences in storage and collection techniques, type of assay, sample site, route of administration, as well as intraindividual variability will result in variable serum levels.[20, 21] Counter-regulatory mechanisms and development of tolerance can complicate the relationship between the plasma concentration of nitroglycerin and its effects.[20, 21] It is also suggested that the pharmacological effects of nitroglycerin could be related to blood vessel wall concentration rather than plasma concentration.[22] Therefore, it is unwise to try to apply pharmacokinetic data obtained with different formulations or routes of administration to predictions on

Table 1
Comparison of Pharmacokinetic Parameters[26, 31]

Delivery System	Onset	$(C_{plasma})_{ss}$ pg/ml* per unit	$(C_{plasma})_{ss}$ pg/ml* per cm^2	Rate of absorption thru skin in vitro $\mu g/cm^2/hr$
Ointment 2% 4" x 4"	30-60 min.	151.3±24.5	15.1±2.4	20.45
Transdermal				
Transderm-Nitro 5	30 min.	130.6±21.7	13.1±2.2	14.55
Transderm-Nitro 10	30 min.	209.8±22.8	10.5±1.1	—
Nitro-Dur 20	30 min.	201.4±60.7	10.1±3.0	16.67<12 hr and 10.50>12 hr
Nitro-Disc 16	30 min.	280.6±18.7	17.5±1.2	20.45

* Concentration in the plasma at steady state expressed in pg/ml.

pharmacological effects, efficacy and duration of activity.[20, 21]

Nitro-Dur (Key Pharmaceuticals) consist of a 2% w/w nitroglycerin in a polymer-gel matrix as its inner layer. The nitroglycerin is in equilibrium between a liquid phase and that absorbed on suspended lactose crystals.[23] Transderm-Nitro (Ciba Pharmaceuticals) is a reservoir system. Nitroglycerin is absorbed on lactose in a silicone medical fluid with silicone dioxide added to increase viscosity. This is enclosed by an ethylene-vinyl acetate copolymer membrane that is permeable to nitroglycerin. The nitroglycerin seeks out an area of lower concentration and passes out of the reservoir through the permeable membrane into the skin.[24] Nitro-Disc (Searle Pharmaceuticals) is a reservoir system which contains microsealed nitroglycerin evenly dispersed in a solid silicone polymer. The nitroglycerin moves from the polymer into a liquid pocket and then it is available to the skin.[25]

Relative skin permeability of nitroglycerin as delivered by transdermal patches was studied by Chien.[26] Table 1 summarizes the steady-state plasma profiles of the patches and expresses them in terms of area of skin treated. Nitro-Disc demonstrated greater bioavailability. Chien also studied the skin permeation of nitroglycerin and found both Nitro-Disc and Transderm-Nitro to have constant delivery over a 30-hour period. Nitro-Dur, however, showed a biphasic pattern with a rate change after 12 hours from 16.67 $\mu g/cm^2/hr$ in the initial 12-hour period to 10.56 $\mu g/cm^2/hr$ in the remaining period. Nitro-Disc's permeation is 25% greater than Transderm-Nitro at 18.15 $\mu g/cm^2/hr$ and 14.55 $\mu g/cm^2/hr$, respectively. Both are higher than Nitro-Dur with an average of 13.62 $\mu g/cm^2/hr$. It was also found that the smaller size Nitro-Disc (8 cm^2) compensated for its higher rate of skin permeation making it interchangeable with Transderm-Nitro (10 cm^2) and Nitro-Dur (10 cm^2) in delivering equivalent amounts of nitroglycerin over 24 hours. A comparison of the pharmacokinetic parameters of the patches and ointment is given in table 1.

Administration, Dosage and Adverse Effects

In the past, the terminology used to describe the various patches has been a source of confusion. The FDA now requires that all manufacturers label the patches numerically by the amount of nitroglycerin delivered over 24 hours. Transderm-Nitro products have always been labeled in this manner, but Nitro-Disc products have just recently met this labeling requirement. Previously Nitro-Disc was labeled according to the total nitroglycerin content (MG). Nitro-Dur products are still labeled numerically according to the size of the patch (cm^2), but will meet the new labeling requirements in the near future. Table 2 compares the patches for size, nitroglycerin content, delivery and cost.

Dosing guidelines for all products are empiric, with relief of angina, the reduction of the number of sublingual

Table 2
Comparison of Nitroglycerin Patches[31, 32]

Product		Size (cm^2)	Content (mg)	Delivery in 24 hrs (mg)	Cost per unit†
Transderm-Nitro	2.5	5	12.5	2.5	$0.92
	5	10	25	5	0.96
	10	20	50	10	1.06
	15	30	75	15	1.16
Nitro-Dur	5	5	26	2.5	0.84
	10	10	51	5	0.88
	15	15	77	7.5	0.90
	20	20	104	10	0.93
	30*	30	154	15	—
Nitro-Disc	5	8	16	5	0.90
	10	16	32	10	0.96

* Not currently marketed in the U.S.
† Cost as average wholesale price as published in the *Redbook* 1984.

tablets taken or the development of side effects as end points.[3] Questions on equivalency between different nitrate dosage forms can only be established by controlled clinical trials. One author suggests that 0.5 inches of nitroglycerin 2% ointment applied over 20 cm^2 every 8 hours will produce approximately equivalent plasma levels with a once-daily dose of Nitro-Dur 20, Transderm-Nitro 10 or Nitro-Disc 10.[27] At this time it is not recommended that the patches be physically cut in order to individualize dosing, since the effect this has on drug delivery is not yet known. When nitroglycerin is discontinued, it should be tapered slowly over 4-6 weeks to prevent potential withdrawal reactions.[28]

The patches should be applied to hairless areas of the body, preferably the chest or upper arm. They should not be applied to extremities below the elbow or knees, to skin folds, scar tissue, burned or irritated areas. The site of patch application should be rotated daily to avoid irritation of the skin.

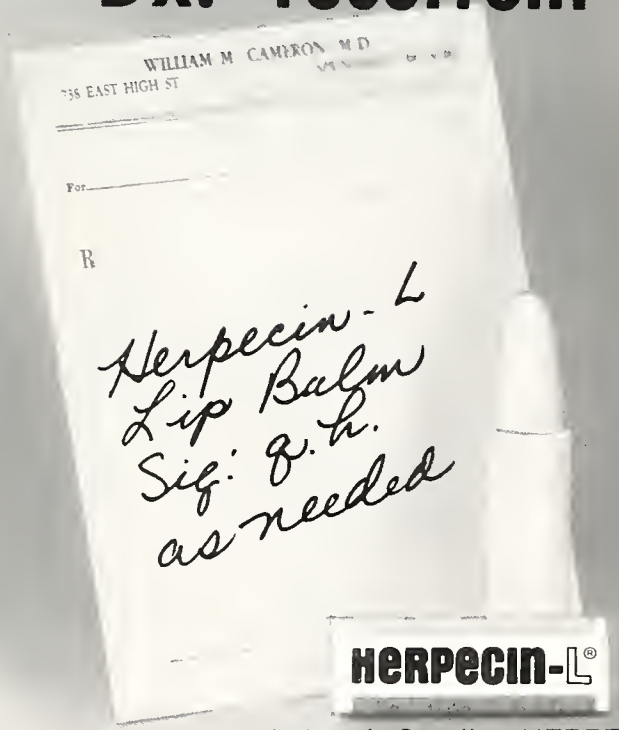
Adverse reactions to the patches are reported to be infrequent. Besides the typical nitroglycerin side effects of headache, low blood pressure, tachycardia, fainting, flushing, dizziness, nausea and vomiting, several dermatologic reactions have been reported.[29] These consisted of contact dermatitis, transient reddening of the skin surrounding the margin of the patch, and one case of a cutaneous burn-like reaction with atrophic changes and scarring possibly caused by the patch.

Conclusion

Transdermal delivery of nitroglycerin holds promise. It is convenient and may provide a means of achieving a sustained nitrate effect. However, at the present time, the data are inconclusive and controversial regarding the twenty-four hour efficacy of the nitroglycerin patches. More carefully controlled studies are required before final conclusions can be made. Clinicians should therefore be cautious when assuming adequate nitroglycerin effects for twenty-four hours in a patient with persistent angina.

References available from the NCMJ editorial office.

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IN STATE

April 15-June 7
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April 24
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April 27
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Place: Chapel Hill
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May 1
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May 23
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Place: Chapel Hill
Fee: $20
Credit: 5 hours Category 1 AMA
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June 13-15
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April 18-20
Radiology Review
Place: Hilton Head Island, SC
Fee: $350
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April 19-21
Seventh Annual Conference on Emergency Medicine for the Primary Care Physician
Place: Williamsburg, VA
Fee: $250
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

April 25-27
Twentieth Annual Pediatric Springfest
Place: Williamsburg, VA
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Letters to the Editor

A Fitting Handle

To the Editor:

I enjoyed and appreciated your editorial, "How the Handle Fit in 1960" in the December 1984 issue of the NCMJ (45:766-7). Your observations and philosophy are equally applicable in 1985. In the field of psychosomatic illnesses you write, "the physician is likely to attribute the symptoms to the area of his own greatest interest." How astute!

I was amused by your using the word "spangle." It's a rare word that could be used more often than it is.

Michael F. Keleher, M.D.
18 Maywood Road
Asheville 28801

EMT Study Guide

To the Editor:

As providers of training for basic emergency medical technicians (EMTs) who wish to become certified at the intermediate level (EMT-Is), we are concerned about the knowledge EMTs possess when they enroll in our training programs. The reason for our concern is that people tend to forget things they learn as time passes, particularly if they do not have opportunities to apply their knowledge. Since our training programs are offered to EMTs in rural areas, we must assume that this factor is operating to a greater extent than in urban areas. Therefore, we have developed a *Study Guide* to help EMTs review material presented in their basic courses and a pretest to provide feedback on the effectiveness of their review.

The primary objective of the review process is to help EMTs prepare themselves to profit from the instruction in the EMT-I Course. To this end, our *Study Guide* was developed by a committee of physicians and nurses with experience in providing emergency medical care, and it is keyed to the text recommended by the North Carolina Office of Emergency Medical Services for basic training programs. This committee also wrote the pretest, the results of which are made available to local review boards appointed by the hospital sponsoring the training program as they consider applicants for the program. We have monitored the performance of EMTs on the pretest and are happy to report that factors such as education, being a paid EMT, or length of service as an EMT have not influenced pretest scores to the extent that potentially successful applicants have been denied training.

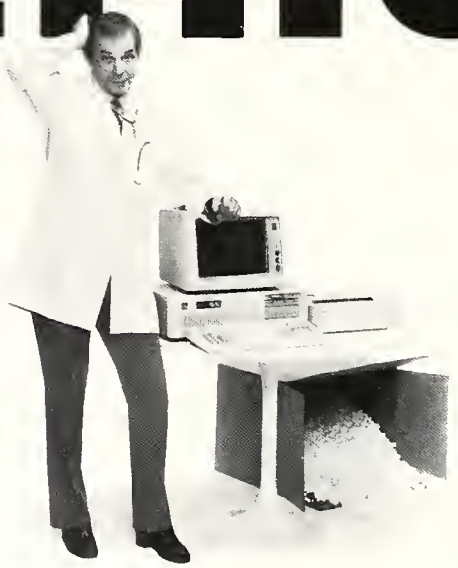
While we cannot prove that the *Study Guide* is the cause of the applicants' high level of performance on the pretest, we believe that the *Study Guide* helps them structure their review of material they learned during their basic training programs and, perhaps more importantly, helps them focus on material that is the foundation of intermediate training. We also believe that the pretest increases the applicant's motivation beyond the level that would be achieved in its absence. Finally, based on the performance of EMTs trained in our programs on the state certification examination, we believe that our process helps us identify EMTs who can be expected to complete our training programs successfully and obtain certification.

We hope to publish a more complete report of our experiences, including supporting data, in the near future. In the meantime, we will be happy to share our experiences and data with interested parties. We also welcome any suggestions for improving the process we presently use.

Sandra S. Landis, RN/MICN
Theodore W. Whitley, PhD
E. Jackson Allison, Jr., MD/MPH
Department of Emergency Medicine
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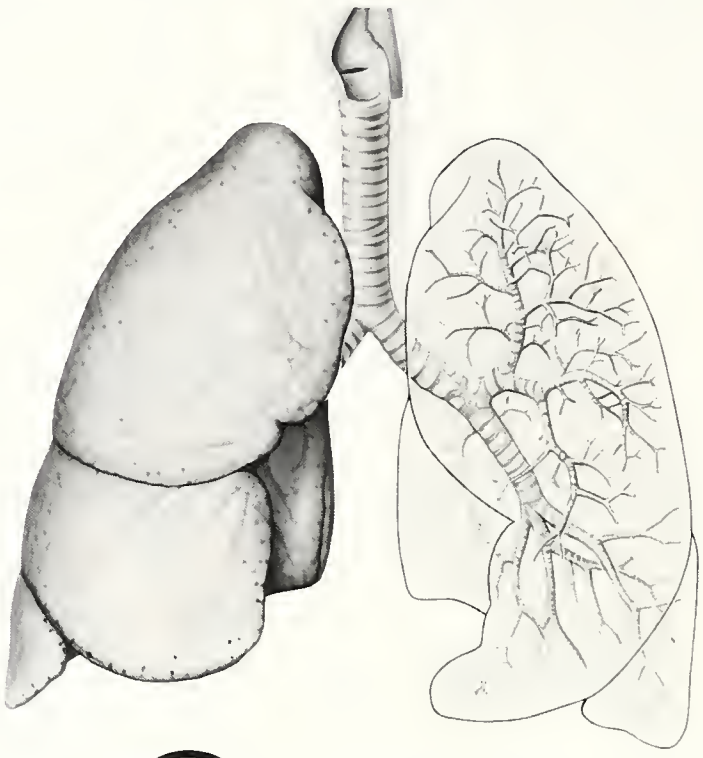
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Brief Summary Consult the package literature for prescribing information

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), *Haemophilus influenzae*, and *S. pyogenes* (group A beta hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions* — If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note: Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

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Winthrop-Breon Laboratories has met a nagging problem by reformulating TALWIN® 50 (pentazocine HCl tablets) with the addition of naloxone, equivalent to 0.5 mg base. The reformulated product is called TALWIN® Nx.

The original formulation had been subject to a form of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ,* an antihistamine, would be ground up together, put into solution, and injected intravenously. The combination produced a heroin-like high. Because naloxone is a narcotic antagonist when injected intravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine in a combination of TALWIN Nx and PBZ. When taken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for the relief of moderate to severe pain, now providing added security against misuse.

*Registered trademark of Ciba-Geigy Corp for tripelennamine.



The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

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Please see following page for Brief Summary.

Talwin® Nx® IV

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence.* Can cause physical and psychological dependence. (See **Drug Abuse and Dependence**.) *Head Injury and Increased Intracranial Pressure.* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Can obscure the clinical course of patients with head injuries; in such patients, use with extreme caution and only if deemed essential. *Usage with Alcohol.* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics.* Pentazocine is a mild narcotic antagonist. Withdrawal symptoms have occurred in patients previously given narcotics, including methadone. *Certain Respiratory Conditions.* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Precautions: *CNS Effect.* Use cautiously in patients prone to seizures; seizures have occurred though no cause and effect relationship has been established. Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours. Such patients should be very closely observed and vital signs checked; if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function.* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient. *Biliary Surgery.* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures, the clinical significance of these findings is not yet known. *Information for Patients.* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction.* Use with caution in patients with myocardial infarction who have nausea or vomiting. *Drug Interactions: Usage with Alcohol.* See **Warnings.** *Carcinogenesis, Mutagenesis, Impairment of Fertility.* No long-term studies in animals to test for carcinogenesis have been performed. *Pregnancy Category C.* Should be given to pregnant women only if clearly needed. *Labor and Delivery.* Use with caution in women delivering premature infants. Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown. *Nursing Mothers.* Caution should be exercised when administered to a nursing woman. *Pediatric Use.* Safety and effectiveness in children below the age of 12 years have not been established.

Adverse Reactions: *Cardiovascular.* Hypotension, tachycardia, syncope. *Respiratory.* Rarely, respiratory depression. *CNS Acute CNS Manifestations:* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted. *Other CNS Effects.* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor. *Gastrointestinal:* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress. *Allergic:* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora. *Ophthalmic.* Visual blurring and focusing difficulty. *Hematologic.* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance.* TALWIN Nx is a Schedule IV controlled substance.

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported. In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient. Tolerance to the analgesic effect is rarely reported; there is no long-term experience with oral use of TALWIN Nx.

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine; however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics. TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Overdosage: *Treatment.* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing.

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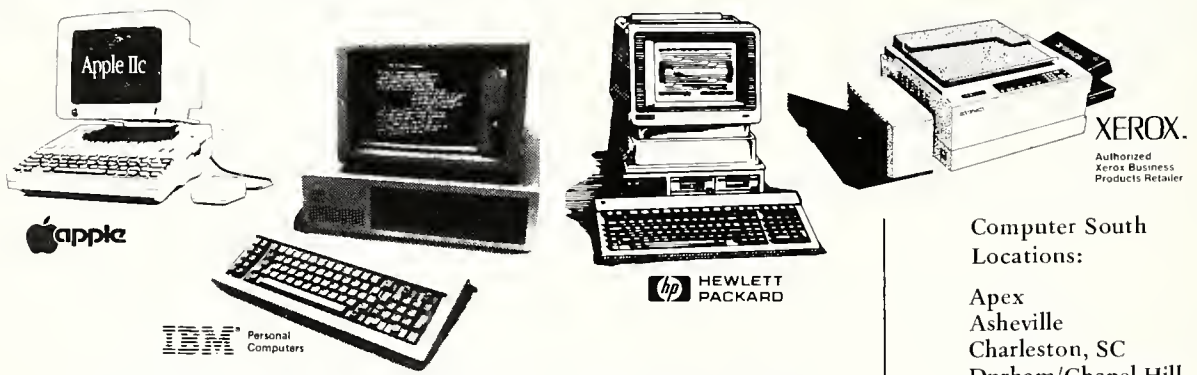
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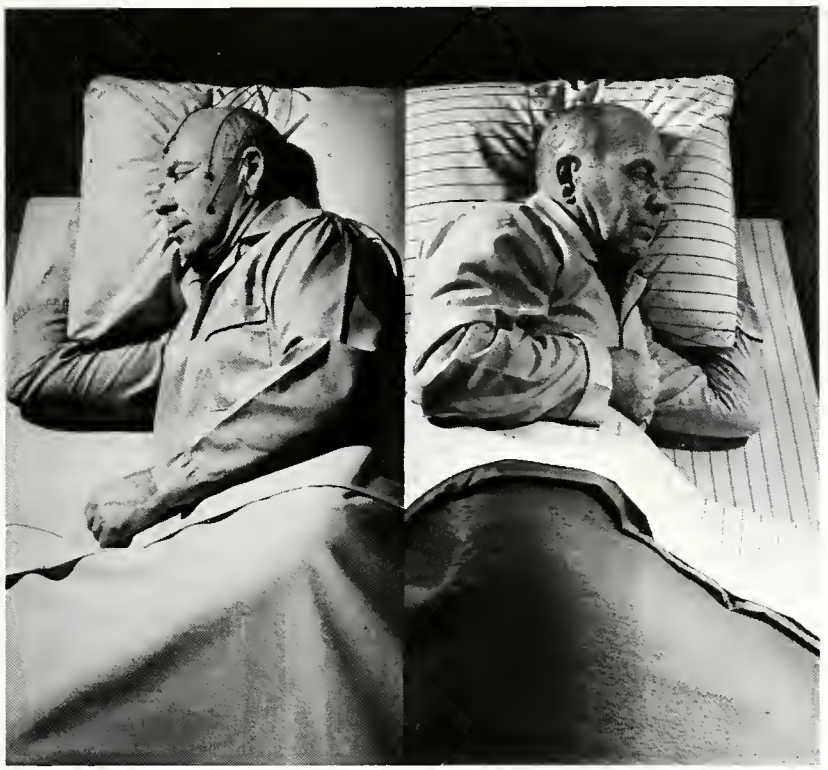
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Caution patients about driving, operating hazardous machinery or drinking alcohol during therapy. Limit dose to 15 mg in elderly or debilitated patients. Contraindicated during pregnancy.

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References: 1. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther* 32:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983. **10.** Monti JM: *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep* 5(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

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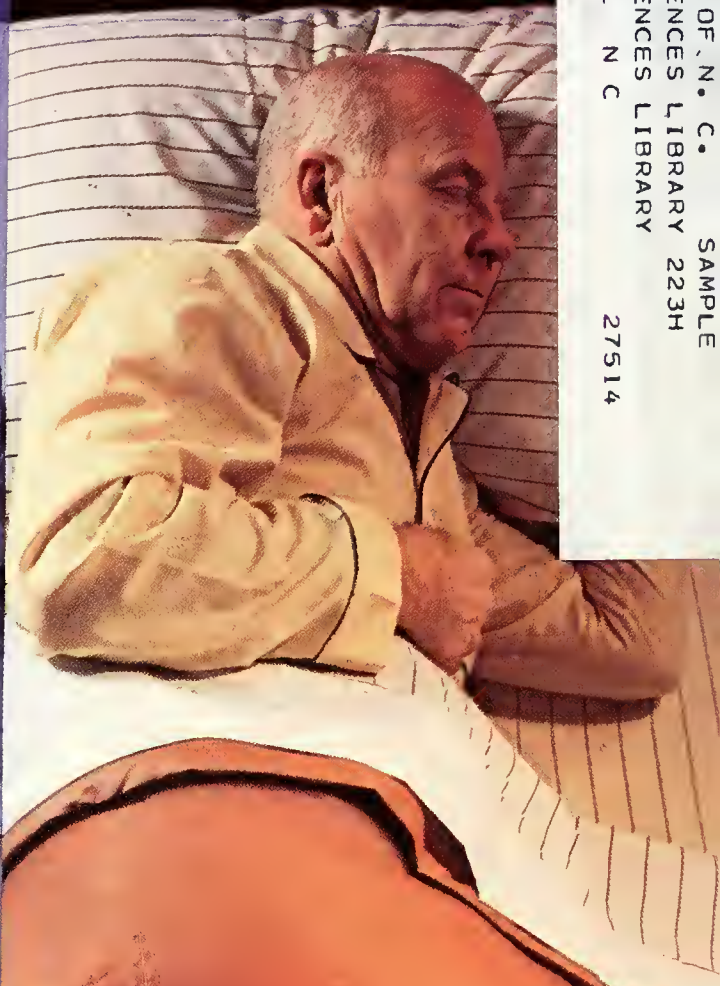
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ETHICS

Protesting the Proposed Federal Regulations for Critically Sick Infants

Loretta C. Kopelman, Ph.D.

• *Regulations proposed by the Department of Health and Human Services to implement the "Baby Doe" provisions of the 1984 Child Abuse and Treatment Act undermine the physician's ability to act in the best interest of the patient.*

MANY members of the Greenville, North Carolina medical community protested a recent and unprecedented attempt by the Department of Health and Human Services to restrict those practicing medicine and keep them from acting in what they believe is the best interest of their patients. The protest against proposed federal rules and guidelines regarding the treatment of severely ill newborns[1] was conveyed by letter to the Department of Health and Human Services. How many actually signed the letter is uncertain. More than 100 copies of it were distributed; some were duplicated, and many were sent with 10 to 30 signatures. I believe several hundred people signed, most of them physicians and medical students.

My purpose in writing this article is to record this protest publicly and permanently, to clarify why I wrote the letter, and to ask others to join us in protesting the proposals. In calling attention to why this letter was drafted, perhaps it will also illuminate why so many within the community were willing to sign it.

Briefly the background is this: The Child Abuse Amendments of 1984 were made to the Child Abuse Protection and Treatment Act, a federal law passed in 1974 establishing the National Center on Child Abuse and Neglect in the Department of Health and Human Services.[2] According to the new amendments, state-based child protection services could investigate charges that severely handicapped infants were suffering medical neglect. The formation of Infant Care Review Committees was strongly encouraged to guard against such neglect and to allow child protection services to work with Infant Care Review Committees. The 1984 Amendments attempt to clarify appropriate services and treatment for disabled infants. They were a compromise worked out by many interested organizations including the American Academy of Pediatrics.[3] These 1984 amendments circumvented a controversial series of attempts to formulate policy through an existing law, Section 504 of the Rehabilitation Act.[4] (A brief summary of these events may be found at the end of this paper.)

Our protest does not concern the law, the 1984 amendments to it or the events leading up to it. Rather, it focuses on the Department of Health and Human Services' efforts to *implement* these new statutory provisions of 1984 by offering rules, definitions and model guidelines for health care providers to establish Infant Care Review Committees. These proposed rules and guidelines for health care providers to establish such Committees, to which we protest, were published on December 10, 1984. The Department of Health and Human Services accepted and recorded comments until February 8, 1985. The new rules and guidelines, however, do not go into effect until six months after publication. With enough protest, we hope they will not go into effect at all. For, however well-intentioned, they could violate an ancient Hippocratic duty to act in the best interest of patients.

I will begin by first reproducing the letter. Second, I will show how I believe the proposed regulations alter the law by offering a different standard, one with less protection to infants singly and collectively. Next the Infant Care Review Committee proposed rules are criticized, and some observations are made about how the proposed rules, unlike the 1984 Amendments, are out of phase with recent important court rulings. The letter follows.

National Center on Child Abuse & Neglect
U.S. Children's Bureau, HHS
P.O. Box 1182
Washington, D.C. 20013

Attention: Jay Olson
Re: Child Abuse and Neglect Prevention and Treatment Program Proposed Rules — Part 1314 (Amended) Issued Dec. 10, 1984

Dear Sir:

This letter conveys opposition to many of the regulations proposed by the Department of HHS to implement the "Baby Doe" Provisions in the Child Abuse and Treatment Act. Our objections are similar to those of the American Academy of Pediatrics and the response drafted by the State of North Carolina, Department of Human Resources, under Secretary Phillip J. Kirk, Jr.

First, we are concerned the HHS definitions distort the law:

(1) **Virtually futile** — The HHS definition of virtually futile treatment is that it is "highly unlikely to prevent imminent death." Inclusion of the word "imminent"

From the Department of Medical Humanities, East Carolina University School of Medicine, Greenville 27834.

goes beyond the law and would require the treatment of an infant, for example, with Trisomy-13, who would die within a month to a year. It should be largely at the discretion of the physicians and the parents to determine whether fully treating such an infant would be in the infant's best interest.

(2) **Life-threatening condition —** The HHS definition of this stipulates that treatment may **not** be withheld "on the grounds that one or more of the infant's nontreatable conditions, although not imminently life threatening, will become life threatening in the future." The word "imminently" amends the law and should be omitted from the definition. For, once again, if the condition of the infant will become life threatening within the forseeable future, then physicians and parents should have the discretion to decide whether full treatment is in the best interest of that infant or will impose inhumane suffering on that child. Inclusion of the word "imminently" limits the range of these judgments.

(3) **Treatment —** The definition expands the intent of the law by including omission of further evaluation as a failure to treat. This again amends the law and restricts the discretion of parents and physicians.

Second, we are concerned about the Infant Care Review Committee guidelines.

(1) The basic functions are said to be optional yet the model is drawn in great detail and the words to describe its functions are "must" and "shall." This creates the false impression that ICRCs are mandated and the given form is prescribed by law.

(2) The functions are so broad that they could require a paid staff.

(3) It is uncertain how established rules of confidentiality and liability apply to the ICRC proceedings.

Third, the "Baby Doe" rulings coupled with the concerns over malpractice, have resulted in the tendency to treat even infants with the most futile prognoses. We are finding most intensive care nurseries filled with very small premature infants whose prognosis is grim, while infants with good prognoses do not get treatment because there is no room for them in the intensive care unit. While hospitals or intensive care units have no strict legal obligation to infants who are not in their units, reason would suggest that some consideration be given to infants who would profit from intensive care by having their lives saved or saved from the ravages of retardation and other handicaps, but who cannot gain access to care.

Fourth, the cost of caring for infants slowly dying over weeks and months in the NICU is great in terms of harm to these infants through their suffering, harm to the infants who cannot gain access to any NICU, harm to the families who watch them suffer and harm to the staff who witness these tragedies. The financial cost is also great, measurable in multiples of tens of thousands of dollars. With limited budgets this has the consequence of making less available to babies whose conditions can be helped, or whose conditions are serious but not life-threatening.

We urge you in the strongest possible way to allow more discretion to parents and physicians in choosing how to provide the most humane treatment for each infant, and acting in each infant's best interest.

Sincerely yours,

Name: Affiliation:

Different Standards

The 1984 Amendments, unlike the proposed regulations to implement them, allow the family and physician some discretion in deciding what is the best interest of a severely handicapped infant. According to the proposed rules, treatment may be withheld from a severely handicapped infant only if the death is imminent or the infant is irreversibly comatose. In contrast, the 1984 Amendments would also allow treatment to be withheld if it would not correct the underlying life-threatening condition, or if in terms of overall harms and benefits the treatment would be virtually futile and inhumane. The law uses a form of the *Best Interest Standard*. According to a Best Interest Standard those deciding for incompetent persons who were never competent should determine as best they can what the interests of the person are and, of those interests, which are most important in terms of the incompetent person's total well-being. When treatment is more of a burden than a benefit, then whether death is imminent or foreseen, it may not be in the best interest of the infant to treat fully. When employing the Best Interest Standards, therefore, one may properly consider whether a somewhat longer life in the Neonatal Intensive Care Unit (NICU), but one filled with suffering from the use and resulting complications of its technical resources, is in the best interest of a very handicapped child; or whether a shorter but more comfortable existence, perhaps closer to the child's family, is in the infant's best interest. Using this standard, it is legitimate to inquire whether it is in the overall best interest to fully treat an infant with Trisomy-13 or a premature infant weighing 700 grams who has had severe intracranial bleeding. Determining the net benefit includes judging if the discomfort of treatment and possible complications from using this technology are harms justified by a long range good for the infant.

The Best Interest Standard, therefore, allows consideration of an array of beliefs, values and preferences. The protection to the infant, however, is that this standard is restricted because its primary focus is on the infant's well-being or rights, and not what overall benefits society or the family might have. Moreover, when applied to infants this standard tends to be especially conservative. Incompetent adults may have expressed values or preferences the surrogate is honor-bound to consider. This is obviously not possible for infants, and in using it as an objective standard, we can only estimate what most would consider reasonable. The Best Interest Standard, however, does allow equity or consideration of the special features of each case in applying rules. It allows us to say what is best for *this* child in *this* situation. And insofar as we can reasonably rank important beliefs, values and preferences somewhat differently, this standard permits the possibility of somewhat different reasoned responses about what is in a person's best interest.

In contrast to this, the definitions proposed by the De-

partment of Health and Human Services change the 1984 Amendments by offering a very different standard which permits little or no discernment or discretion in its application. This ruling as implemented by these proposed definitions allows withholding or withdrawing of treatment only where death is imminent or the infant is irreversibly comatose. Little discretion is permitted to families or physicians, and no consideration may be given to the severity of unavoidable and sustained pain.

Less Protection for Each Infant

Even if we agree that the 1984 Amendments and the definitions to implement the law proposed by the Department of Health and Human Services employ different standards, then what practical difference does this make? Both seek the protection of infants. But protection on each standard means different things. According to the 1984 Amendments, the Best Interest Standard allows protection to include a variety of interests including how much suffering is likely from a somewhat longer existence. On the other hand, the proposed definitions recognize protection to mean only one thing: saving all who can possibly be saved up to the limit of technology unless their death is "imminent" or they are permanently comatose. A standard emerges from these proposed rules that is problematic. Though death may be foreseen, overtreatment and overevaluation of infants may be required by law simply because death cannot be known to be "imminent." More basically, however, it disallows the wide considerations possible using the Best Interest Standard. If we agree, however, that a life filled with pain is worse than one filled with happy experiences, and a life filled with potential is better than one that is not, then we can legitimately consider that a short comfortable life, perhaps at home or free from invasive painful technology, would be better than a somewhat longer, painful one. If so this would allow considering that it is in someone's best interest to forego full treatment.

Therefore, the Department of Health and Human Services' definitions distort and amend the law by offering a different standard for the treatment of handicapped infants. In addition, the Department's standards are unjust because they allow parents and physicians no opportunity to consider important features of the situation, such as how much suffering the baby will be forced to endure, in making their judgments.

It is disturbing to be kept from acting in a way one believes is in the best interest of the patient because the patient objects to treatment or because there is no treatment available. But it is more distressing when restrictions intended to protect cause harm. What is deeply troubling about the proposed rules is that, however well intentioned, they seem to violate the ancient Hippocratic moral rule to try to act in the best interest of one's patients. This moral duty and the standard offered by the proposed rules can conflict when considering the best interest of infants singly and collectively.[5] How would these proposed rules affect sick infants as a group?

Scarcity and Protection of All Infants Collectively

If the goal is to protect all handicapped infants collectively as well as each individual patient singly, the intent of the 1984 Amendments has been defeated by the proposed rules of the Department of Health and Human Services. Physicians and hospital administrators, mindful both of malpractice litigation and of federal laws and guidelines, are inclined now to overtreat or overevaluate all infants, even those with the most futile prognoses. The consequences are that most neonatal intensive care units are filled with such infants slowly dying, and infants with good prognoses cannot gain access to these units. Intensive care may be thought of as a "scarce resource," and we have to determine how best to distribute it among a population. Is it reasonable to insist that the baby born with Trisomy-13 or severe intracranial bleeding, who we know will die but whose death is not "imminent" must, in spite of the good will judgments of parents and physicians, be fully treated over weeks or months until his death is "imminent"; while an infant with a good prognosis who, with a few days in the nursery, might lead a healthy normal life must be denied?

Infant Care Review Committee

The Department of Health and Human Services has also recommended *as optional* the formation of ethics committees or Infant Care Review Committees. State-based child protection services would seek the assistance of such a committee to investigate charges of medical neglect. The Department uses great detail to present one particular model for the Infant Care Review Committee. This detail and employment of the language of "must" and "shall" tend to defeat the comment that such committees are optional, giving the false impression that the form and duties of these committees are prescribed by law. In reading these proposed guidelines, one is reminded of the committees required to review all proposed human research at institutions receiving federal funds. *If* the Infant Care Review Committee were like these Institutional Review Boards, then each committee would be legally obligated to review, approve or disapprove life and death decisions just as Institutional Review Boards must approve or disapprove research projects. That is, the Infant Care Review Committee in these proposals appears like a watchdog committee required to "pass" on each "proposal" like the Institutional Review Board.[6] But this seems quite inappropriate especially since the courts have repeatedly argued that the primary decision maker for judging the well-being of incompetent persons is the parents with the advice of the physician.

It is useful to have committees that will help to form policy and educate, to offer assistance to physicians and families in making these decisions, to consider the alternatives, prognosis, and resources in a particular situation, and to help those with questions of certain sorts. In an area where so little has been done, however, we should want many models tried, in the hope that from the variety we will learn what tends to work. It seems likely to me that the best committees will focus on what is the best for the infant. Fear of litigation and malpractice, however, could distort these judgments. Therefore some states, such as Arizona, have taken the additional step of making it possible for these committees to function without such fears by allowing the members of these committees immunity from prosecution, and mandating that its records and deliberations are nondiscoverable.[7]

It is disturbing when the judicial and administrative branches of government seem to recommend different standards as policy. In proposing to implement the 1984 Amendments with such restrictive rules the administration moves to *reduce* the discretion of families and physicians in making decisions for incompetent individuals. The New Jersey Supreme Court in January 1985 moved to *extend* their discretionary power. The New Jersey Supreme Court, which in 1976 allowed Karen Ann Quinlan to be removed from a respirator, handed down another landmark and controversial decision regarding Claire C. Conroy. In the Quinlan case the court argued that all life support can be withheld from incompetent as well as terminally ill competent patients, provided that is what the patient wants or would want. In the Conroy case the court reversed a ruling by the lower appellate court which had ruled that removing the feeding tube of an 84-year-old patient named Claire C. Conroy would have constituted homicide. Ruling 6 to 1, the justices said it was not homicide and clarified how the decision to stop treatment may be made for elderly, terminally ill patients, particularly those in nursing homes. The court said that when the patient's wishes cannot be determined, the family and physician should consider whether life-sustaining treatment would place burdens on the patient that outweigh the benefits derived from life and also whether the pain suffered would be "inhumane." This extends the discretionary power of families and physicians. In the past the law had applied only to individuals who are brain dead or who, like Karen Quinlan, are irreversibly comatose.[8]

The Conroy Court reaffirmed the discretionary power of the family and the physician, and the person's right to refuse all medical care even at the risk of death, and found there is no difference in principle between the decision to begin treatment and the choice to stop it. The Court argued that physicians should not be fearful to discontinue respirator therapy once it has been started if discontinuing the therapy is in *the best interest of the patients*. The Court ruled that drawing a sharp line between feeding and providing other kinds of care may be inappropriate. While the Conroy Court is not meant to apply to newborns, it raises some important questions. First, if we should not discriminate on the basis of age, then we should either allow non-treatment of severely compromised infants if it is in their best interest to do so, as we do for elderly incompetent persons, or we should insist that all be treated unless their death is "imminent" no matter how much they suffer. Second, the Conroy Court distinguishes several Best Interest tests, one of which is similar to that discussed herein. This test, called the Pure-Objective test (unlike the limited-objective and subjective tests), has no evidence to consider about what the individual would have wished, but can only consider if the benefits of treatment outweigh its harms or if "the recurring, unavoidable and severe pain of the patient's life with the treatment should be such that the effects of administering life-sustaining treatment would be inhumane."[9]

Third, the Conroy Court is from New Jersey, and New Jersey led the way in the formation of ethics committees following the Karen Ann Quinlan decision. The Quinlan Court ruled that an ethics committee would be of value in New Jersey hospitals to determine the accuracy of the diagnosis and prognosis and to help spread the responsibility for these difficult decisions. These committees have worked well, perhaps because they are seen as a resource for families and physicians and because they are protected by the courts. The Conroy Court has ruled ethics committees may use these Best Interest tests.[9]

The Conroy Court gives importance to the Best Interest Standard and allows it to be applied in several different ways. It seems compatible with the 1984 Amendments to the Child Abuse and Treatment Act, but incompatible with the standard offered by the Department of Health and Human Services' proposed rules. In protesting the newly proposed definitions and guidelines, we suggest the proper standard to use is that of trying to do what is in the best interest of the incompetent person.

Although the time for official comment on these proposed regulations to implement the Child Abuse Prevention and Treatment Act has passed (the deadline was February 8, 1985), perhaps it will still be useful for others to make their views known.

*Brief Background**

1973 Rehabilitation Act containing Section 504 signed into Law by President Gerald Ford. (P.L. 93-112.29 U.S.C. 74)

1974 Child Abuse Protection and Treatment Act signed into law by President Ford establishes the National Center on Child Abuse and Neglect. (P.L. 93-247, 42 U.S.C. "5101 et seq.)

May 18, 1982 Rehabilitation Act of 1973 was used as a legal basis for the HHS Notice to Health Care Providers in 6800 hospitals.

March 7, 1983 HHS publishes the "Interim Final Rule" in *Federal Register*. They take effect March 21, 1983.

April 14, 1983 American Academy of Pediatrics vs Heckler. No. 83-0774, U.S. District Court, D.C. Judge G. Gesell of the US-DC Court invalidates the interim ruling because:

1. the time required for comment was denied;
2. no definition is given of the "customary medical care";
3. it is "arbitrary and capricious" in failing to consider existing means of protection;
4. the free hotline is "ill-considered" and "open to misuse";
5. the investigators might jeopardize quality NICU care.

January 12, 1984 HHS publishes Final Rules in the *Federal Register* "Nondiscrimination on the Basis of Handicap; Pro-

cedures and Guidelines Relating to Health Care for Handicapped Infants'' (Vol. 49:8, 1622-1654).

February 23, 1984 U.S. Court of Appeals for the Second Circuit denied the government access to ''Baby Jane Doe's'' records.

March 12, 1984 The American Hospital Association brings suit in the U.S. District Court for the Southern District of New York, challenging the applicability of Section 504 of the 1973 Rehabilitation Act as the legal basis for the HHS rule.

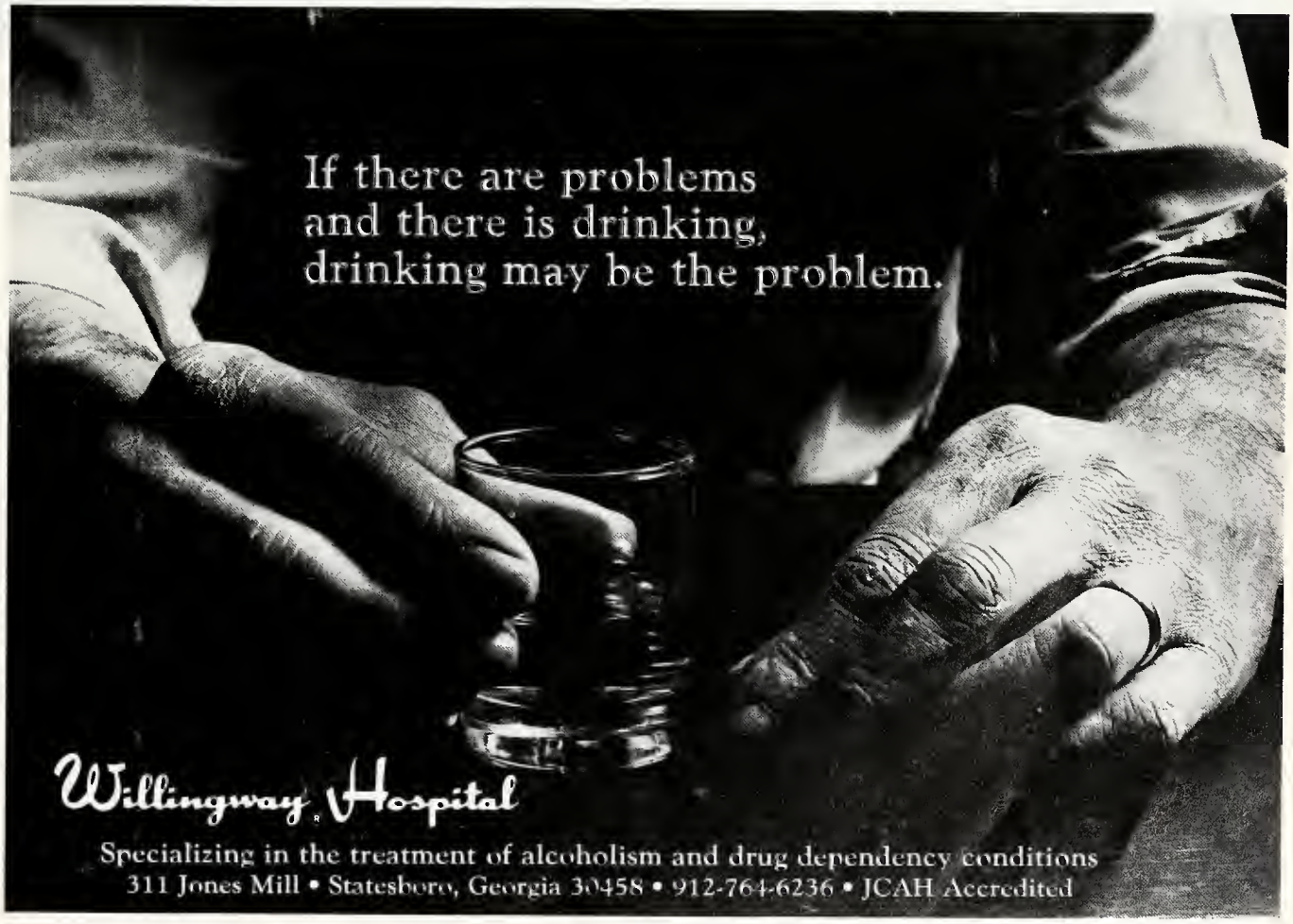
October, 1984 President Reagan signs a compromise bill into law: Child Abuse and Neglect Prevention and Treatment Program. The 1984 Amendments to the Child Abuse and Treatment Act of 1974.

December 10, 1984 The Department of HHS proposes rules to implement this law.

* Some references to read for a fuller background are: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research *Deciding to Forego Life-Sustaining Treatment*. Especially note the chapter, ''Seriously Ill Newborns,'' pp. 197-229. AND Weir, R. *Selective Treatments of Handicapped Newborns*. Oxford University Press, Oxford, 1984.

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Physicians' Forum: Medical Direction and Accountability for EMS Advanced Life Support Care in Rural North Carolina

Jane M. Hartley, M.S.P.H., Sandra S. Landis, R.N. and E. Jackson Allison, Jr., M.D., M.P.H.

• *How ECU's Emergency Medicine Department overcame the problem of involving area physicians in the development of a rural emergency medical services system.*

TO develop medical leadership and cooperation for prehospital emergency medical services in a 29-county area of eastern North Carolina: this was our assignment. The first move was to establish a non-profit organization, Eastern Carolina Emergency Medical Services, Inc. (ECEMSS), to raise funds for the venture. Federal dollars were obtained by June 1981.

A review of the geography emphasized the magnitude of the problem. The 29 counties cover approximately one-third of the state and measure roughly 150 miles from north to south and 160 miles from east to west at their most distant points, or approximately 13,736 square miles. The latest census has shown the population to be fairly stable at just over one million. Population is sparse in the majority of these counties with the average density being less than 75 people per square mile.

Approximately 35 percent of the total population is nonwhite with a low socioeconomic status, which is highly correlated with poor health.[1] Chronic illnesses and emergency cases put a strain on the emergency medical system and the region's hospitals.

Within the area are 23 general hospitals with various levels of emergency department coverage. In general, there is only one hospital in each county and the advancement of emergency medical services is not high on its list of priorities. Thus, between volunteers who do not have the training and equipment and hospitals that lack many necessary equipment and personnel requirements, advanced life support in the region has developed very slowly.

To develop medical leadership and cooperative efforts between hospitals and emergency services, the non-profit corporation and the Department of Emergency Medicine at East Carolina University School of Medicine co-sponsored a quarterly evening gathering called the "Physicians' Forum." The initial group that was invited included individual physicians who had assumed key roles in established EMS advanced life support programs. As medical directors and chairmen of audit and review committees, these physicians had been willing to get involved with their local rescue squads and hospitals to ensure that the programs were organized and initiated.[2]

At the first gathering, which was held in February 1981, there were physician representatives from the seven counties participating in EMT-I programs. All seven programs were comprised of volunteers or paid/volunteer memberships that had been trained to the EMT-I level by the Department of Emergency Medicine at East Carolina University School of Medicine. Each has one medical care facility, i.e., sponsor hospital,[3] in its respective county to which the majority of its patients are transported. All the programs were established under the Rules and Regulations, Mobile Intensive Care Program, North Carolina Office of EMS, and were certified by that agency. Yet with all these similarities, none of these physicians had met previously to share their experiences, especially in a group.

While the consensus is that emergency physicians make the most appropriate leaders in the field of EMS,[4] there is little opportunity for these individuals to acquire, much less to share, the necessary knowledge and skills outside of a designated emergency medicine residency training program.

The development of a successful EMS system profits by a cooperative arrangement between medical centers.[2] This requires an open dialogue, which became the first achievement of the Physicians' Forum. The physicians were able to compare notes and to discuss mutual problems without bureaucratic direction or guidelines. This prevented each program from wasting precious time trying to "reinvent the wheel." Instead, they hammer out the best way to solve programmatic issues together.[5] "A number of people throughout the country have the same instincts — it makes no sense to work [out problems] in isolation."[6]

Through the quarterly meetings held in the past four years, several regional issues have been identified as common concerns to all. Retrospective review of these topics finds that they logically fall into three primary categories: 1) communication channels with the North Carolina Office of Emergency Medical Services; 2) standardization of EMS system development; and 3) projects appropriate to EMS

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personnel in Area VI.

In North Carolina, the Office of Emergency Medical Services is charged with monitoring and enforcing the Rules and Regulations as promulgated by the State Board of Medical Examiners. NCOEMS also serves as the advisory organization to the Board of Medical Examiners.[7] Medical control in all ALS programs, therefore, is controlled by these two organizations. Before the advent of the Physicians' Forum, physician input from the field to these agencies had been sporadic, particularly in the East, and no clear avenue for expression of clinical concerns had been identified.

The disadvantages of lack of direct access to NCOEMS regulatory committees became obvious when the Forum members addressed a common clinical topic. The esophageal obturator airway had been accepted by NCOEMS for use by EMT-Intermediates, while the newer state-of-the-art adaptation, the esophageal obturator airway with gastric tube modification — the esophageal gastric tube airway — had been disallowed. This decision had eliminated physician option and control. Expressions of concern by individual physicians on the matter had been ineffectual; therefore, the Physicians' Forum decided to attempt a united statement to the Medical Director of NCOEMS. The result not only established a format for improved interchange, it also provided direction for future communications between both parties; in addition, the esophageal gastric tube airway was accepted by NCOEMS for EMT-I utilization.

Recognition of advanced life support personnel across county lines and co-sponsorship of advanced life support squads by two sponsor hospitals in the region were achieved through action by the Forum.

The second category of issues dealt with the standardization and coordination of the EMS system development within the 29 counties of eastern North Carolina. Federal funding stressed the need for coordinated standards for emergency patient transfers between facilities and provided funds for the development of Emergency Patient Care Transfer Protocols. Several critical care consultants, one from each critical care category — emergencies related to poisonings, burns, trauma, neonates, cardiac patients, spinal injuries and behavioral disturbances — were hired to create germane protocols for the region. The Forum was used to obtain a review of these protocols by the physicians in the 29 counties.

During the preparation and review of these transfer protocols, several Forum members from the larger receiving hospitals expressed concern regarding the total absence of transfer agreements between hospitals in the region. Consequently, the group developed written and signed agreements between transferring and receiving hospitals which clarified necessary and expected transfer procedures, and thereby tightened a very haphazard system of patient transfer. The agreements did not, however, affect existing referral patterns. To create a standardized format, a subcommittee of the Forum was formed which developed an acceptable document for the 29 counties.

Upon the completion of the transfer protocols and transfer agreements, it was the consensus of the Forum that both documents would not be given due consideration if they were sent blindly to each of the 23 hospitals in eastern North Carolina; therefore, it was decided that Dr. Allison and other Forum members would take the documents to each of the area's medical staff meetings to promote understanding and acceptance through appropriate in-service. This process took much longer to accomplish than anticipated and resulted in a great deal of discussion among area medical staff members; however, the result was successful in alerting area physicians that such documents existed and why they were needed.

The need for special projects appropriate to EMS personnel was identified as the third category by the Physicians' Forum. Dedication to the development and coordination of educational opportunities is of foremost concern to all the Forum members; at the beginning of each Forum meeting formal presentations on various topics in emergency medicine for continuing medical education (CME) credit have been added. Furthermore, the scheduling of regular Advanced Cardiac Life Support and Advanced Trauma Life Support courses at East Carolina University School of Medicine has made these courses available for physicians throughout the region.

The Forum was effective in maintaining physician leadership in the use of military antishock trousers (MAST). In North Carolina the basic EMT is permitted to use MAST at his/her discretion as a treatment or stabilization modality. Although NCOEMS encourages medical direction prior to application of the garment in the field, there is no specific regulation specifying the clinical use of MAST in North Carolina. When the regional EMS Councils requested MAST training for their rescue squads, the Forum members expressed their concern about the obvious lack of medical control in the clinical application of the garment. Through a unanimous effort, all protocols for MAST now require EMTs to contact a physician prior to inflation.

The Forum members also participated in MAST in-service sessions which were conducted in three of the four planning regions. This exposure was the first participation many of the members had had with basic EMTs in an educational setting, and they became acutely aware of the real need for physician involvement with this group. The result has been for Forum members to identify area physicians who have shown some interest in the basic life support rescue squads, and to invite them to the Physicians' Forum. Through exposure to and encouragement from the members of the Forum, we hope that these physicians will continue to develop appropriate medical direction for basic rescue squads in eastern North Carolina. Also, more physicians are being invited to attend and instruct in the area's EMS seminars, increasing their visibility with the squads. Due to the size of the area, and the historical paucity of involvement by physicians, we expect that the process of re-education will keep the Forum members occupied for some time to come.

Prospects for the Future

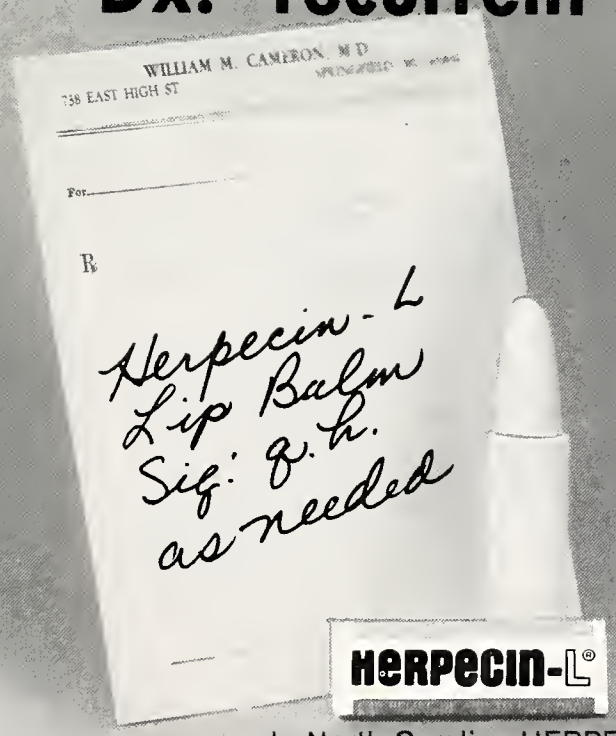
As one might expect, new issues in rural EMS system development continue to surface.[8] Cooperation is a key component for success.[9] Presently the Forum is working with the effects of Level II (and eventually Level I) Regional Trauma Center Designation at Pitt County Memorial

Hospital; the loss of federal monies for EMS development; and the need for rapid transport (i.e., a helicopter service) for severely ill and/or traumatized patients. As in the past, these issues were regional in impact. Now, however, our 29 counties have an effective mechanism in place for their development, resolution and implementation.

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The Impact of Prospective Payment for Physician Fees on Medical Specialists

J. Griffith Steel, M.D.

- *How will the medical profession respond when (or if) DRGs are extended to cover physicians' fees as they now cover hospital fees?*

WHEN President Reagan signed into law PL 98-21 on April 20, 1983, this Social Security reform bill revolutionized the manner in which the Federal government purchased health care for 30 million beneficiaries of Medicare. It ended the "cost-plus" method of reimbursement for hospital services under the Medicare insurance system and introduced a system of prospective payment in an effort to halt the rapidly spiraling costs of health care.

This article examines the impact of the Prospective Payment System (PPS) should it be extended to include payment for physician services and discusses possible adaptive changes in the practice patterns of medical specialists.

The Prospective Payment System

Part B of the Medicare Trust Fund, which reimburses physicians, is the third largest federal domestic program and is the fastest growing entitlements program. It has a compound growth rate over the last several years of 13%, double that of general inflation.[1] The causes for the explosion in health care costs have been extensively analyzed.[2-4] The aging population, increased societal expectations, improved treatment modalities, fear of malpractice, and lack of economic incentives for efficiency all contribute to price and service inflation.[3]

Public Law 97-248, passed in August 1982, ordered the Secretary of Health and Human Services to design and to send to Congress a new payment system for Medicare. On December 28, 1982, the Department presented its proposal (PL 98-21), the most important provision of which was that it fixed in advance a price that Medicare would pay a hospital to treat a particular disease. The impact of the PPS in the first year of phase-in has been significant. After rising more than 4% annually for years, Medicare hospital admissions remained flat at 8.8 million in Fiscal Year (FY) 1984, despite a 2% rise in the over-65 population (*Business Week,* October 15, 1984). The Medicare hospital budget estimates for FY 84 were revised downward from $41.7 billion to $39.6 billion. Average length of stay dropped from 9.4 days in July 1983 to 7.4 days in July 1984.

From the Eastern Carolina Neurological Associates, Inc., 425 Stantonsburg Road, Greenville 27834.

PPS for Physician Fees

Medicare and Medicaid spent 54 billion dollars, or 64% of its budget, for hospital services in FY 83. The remainder was spent on nursing care, rehabilitation, prescriptions, equipment, and physician fees. Aware that large aspects of the Medicare program remained uncontrolled, Congress required in PL 98-21 that the Secretary of Health and Human Services report on the feasibility of including physician fees under some kind of PPS. The Health Care Financing Administration is actively studying ways of bringing physician fees into a PPS. Brandeis University Health Policy Center is under contract to study whether physician fees should be included in the present Diagnosis Related Group (DRG) system. A study by Mandex, Inc. addresses the issue of how many physician charges before and after hospitalization should be included in a DRG. A system of classifying outpatients based on health resource consumption was developed at Yale University to serve the same purpose as DRGs.[5] Outpatient DRGs, known as "Ambulatory Patient Related Groups," incorporate factors that pertain to patient care, in addition to diagnosis. Fetter assessed 70 different variables to find the items that best explained the statistical variance in resource usage for a given diagnosis (Fetter RB: Ambulatory Patient Related Groups, unpublished manuscript, Yale University, 1980).[5] An APG classification system would allow standardization of payment for outpatient care.

In addition to developing a classification system for outpatients, the Health Care Financing Administration is studying new methods for distributing physician fees under a single-payee system. Options include the following:

1. pay the hospital the total service fee and let the hospital pay the physician his share;
2. pay the physician and let him return to the hospital its share;
3. pay the primary care physician the entire sum and let him distribute shares to the hospital and consultants.

Implications for Medical Specialists

Medical specialists constitute approximately 28% of all physicians (internal medicine, allergy, cardiovascular diseases, dermatology, gastroenterology, pediatrics, pediatric allergy, pediatric cardiology, and pulmonary medicine).[6]

Excluding the pediatric group, medical specialists spend 44% of their patient contact hours in the office and 26% in the hospital, compared with 58% and 15%, respectively, for general and family physicians.[7] They depend heavily on referrals from other physicians; internal medicine and its subspecialties (including neurology) see 63.7% of patients on referral, as opposed to 7% for family and general practitioners.[8]

Under a single-payee, fixed reimbursement system for physician fees there will be a strong economic disincentive for physicians to consult specialists. Hospitals, if allowed to keep part of the savings resulting from reduced physician costs, may hire more staff physicians in order to directly control physician services. Medical entrepreneurs have already used this economic incentive for their profit. Philadelphia-based United States Health Care Systems, Inc., a large for-profit HMO, monitors its physicians' use of specialists. If a physician can provide care without making referrals to specialists, some of the savings goes to him.[9]

Adaptations by Medical Specialists

Regardless of whether the payée is the hospital, a fiscal intermediary, or the primary care physician, consulting specialists will face a decline in demand for their services under a fixed-reimbursement, single-payee system. A number of adaptive changes are foreseeable.

1. **Growth of contract medicine.** Hospitals and physicians will join chains or organized groups.[4, 10] Specialty-based groups are likely to contract their services for a fixed fee in order to assure a patient population.
2. **Vertical integration.** Specialists will expand their services to retain patients who might otherwise be lost back to the primary practitioners. An example would be a cardiology group that offered outpatient diet counselling and cardiac rehabilitation, or a neurology group that expanded to offer office physical therapy.
3. **Horizontal integration.** Specialists will seek to attract outpatient self-referrals, by-passing the primary care physicians. An example would be a free hypertension screening clinic offered by a cardiology group, promoted by aggressive advertising.
4. **Increased medicine by protocol.** With revenues fixed for a given diagnosis, medical specialists within a community or provider group will work out agreed-upon standards of care to enforce uniformity and to maximize economic return. One partner's expensive idiosyncracies may not be tolerated by the group.
5. **Decreased purchase of new technology.** The absence of a mechanism for capital cost and new technology pass-through may act as a disincentive to invest in new equipment.
6. **Hospital substitutes.** One of the most radical and cost-saving innovations would be the creation of alternatives to hospitals for those patients requiring minimal supervision. Large referral specialty groups may invest in motels or apartments to house their out-of-town patients while they undergo diagnostic studies or outpatient treatments.
7. **Sole providerships.** Where possible, medical specialty groups may merge to eliminate competition and increase their bargaining power with fiscal intermediaries.

Comment

The success of the Medicare PPS will doubtless encourage Congress to order extension of the concept to cover physician fees. Beneficial effects include elimination of irrational variation in fees and elimination of excessive reimbursement for procedure-oriented as opposed to cognitive services.[11] A single-payee system will strengthen the role of the primary care physician as the gatekeeper of health services and may encourage medical students to choose family practice as opposed to one of the overcrowded specialties.

In response to the changing economic environment, medical specialists are likely to alter their practices to attract self-referrals, retain patients longer, eliminate competition, contract with large payer-organizations, and create alternatives to hospitals. Practice uniformity among members of specialty groups will be mandatory to minimize costs. However, a physician-PPS which rewards primary care providers for not consulting is fraught with quality of care issues. Competition between specialists and primary care physicians for patients and increased malpractice costs may reduce savings expected from a Prospective Payment System for physician fees.

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Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of symoathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

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WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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The Dark Night of The Soul — Disulfiram Toxicity

Ronald B. Mack, M.D.

HAVE you ever fantasized that you would have liked to live in an earlier time in history? I bet you have! No, I don't mean reincarnation — I mean thinking about what it would have been like to live in the Golden Age of Pericles or the Renaissance or to have worked with Pasteur. I have many favorite eras that I would like to have lived in, but one of my most fervent desires would be to have been a young adult in the 1920s. For example, I could have helped my father in his troubles with the gangs of Bugsy Moran and Al Capone in Chicago — the "beer wars," the "territorial wars" terminating in the St. Valentine's Day Massacre. I could have frequented "speakeasys," danced the Charleston, swallowed goldfish and dated a "flapper" (for those of you who do not understand this, ask your parents or grandparents).

The author who probably fictionalized this era the best was F. Scott Fitzgerald. He personified in his writings and lifestyle the Roaring Twenties, the Jazz Age, the age of America's adolescent rebellion. It was that time after World War I when our country lost some of its innocence. Many of the authors of that time (Hemingway, Fitzgerald, etc.) attempted to chronicle what came to be known as The Lost Generation.

As with many authors of his day, Fitzgerald lived fast, consumed far too much alcohol and did it too often and died too young. It seems that World War I erased many of the conservative pre-war mores in lifestyle and literature. One of his most memorable pronouncements was, "In a real dark night of the soul it is always three o'clock in the morning, day after day." Haven't we all at some time or another found ourself awake at 3:00 am in bed staring into the darkness and having all of our fears inordinately exaggerated? F. Scott Fitzgerald, to my knowledge, did not take disulfiram (Antabuse) to ease his problem with ethanol and he apparently experienced "dark nights of the soul" too numerous to count.

Disulfiram is used by almost a quarter of a million alcoholic patients. It is an aversive drug, which means that if you take it and then consume alcohol you get about as sick as you ever want to be. As with a great many scientific advances this product was discovered by accident. Two Danish physicians were investigating disulfiram's use as a potential antihelmintic. They took some of the drug themselves (Why?) and then proceeded to go to a cocktail party. You can guess the end of the story; the rest is history, as they say.

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

When someone imbibes ethanol, the liver normally metabolizes it by reducing serum levels approximately 15 mg/dl per hour and produces *acetaldehyde* which is a toxic intermediary metabolite. This acetaldehyde is then metabolized by aldehyde dehydrogenase. Disulfiram acts by inhibiting hepatic aldehyde-NAD oxidoreductase (Gosh, I didn't know that, did you?) causing great increases in blood acetaldehyde levels following ethanol ingestion. When you administer ethanol to someone who has been pre-treated with disulfiram the blood acetaldehyde concentration rises five to ten times higher than someone who does not have Antabuse on board. So what — you may inquire!! Well, the effect can be devastating and one of the names of the condition it causes is the *acetaldehyde syndrome* — surely "a dark night of the soul."

Within minutes after imbibing ethanol the disulfiramized patient wishes he or she could enter a time warp and undo this unforgettable event (please remember that we are not just talking about the swallowing of Jack Daniels or Coors, but many other sources of ethanol, e.g., there are over 700 pharmaceutical liquid preparations such as decongestants, cough medicines, etc. that contain ethanol as a solvent or diluent). After a few minutes, the victim experiences a hot, flushed face. Vasodilatation spreads to involve what seems like the entire body causing vigorous throbbing in the head and neck and a pulsating headache (worse than any "hangover" I'm sure). This is accompanied by respiratory difficulty, nausea, profuse vomiting, diaphoresis, chest pain, remarkable hypotension and orthostatic vertigo, diplopia and confusion. Shock would not be unusual. In addition to increasing the level of acetaldehyde, disulfiram is known to inhibit dopamine-beta-hydroxylase which causes a decreased production of norepinephrine in sympathetic nerve terminals and thus hypotension. As little as 7 ml of ethyl alcohol in a sensitive adult can cause a mild version of the above syndrome. This aversive response can last from 30 minutes to several hours. Sometimes the result is death.

Now what do you suppose happens when an adult drinks disulfiram in overdose and does not also drink ethyl alcohol!! This drug is rapidly and completely absorbed from the gastrointestinal tract. Approximately 50% of the drug and its metabolites are eliminated in the urine, feces and breath within 25 hours and after 6 days up to 80% is eliminated; it is highly lipid soluble. Taken by itself disulfiram can cause, in adults, urticaria, fatigue, tremor, reduced sexual potency, tremor, dizziness, epigastric pain, vomiting and diarrhea, a garlic-like taste — wow, am I glad to hear that, I thought it came from the vino rosso and the lobster fia

diavolo!! In general, in adults a single dose of disulfiram, in the absence of alcohol, usually does not produce noticeable side effects except possibly for an initial period of lethargy. On the other hand, carbon *disulfide,* a metabolite of disulfiram, can react with the coenzyme pyridoxine phosphate to inhibit the enzyme monoamine oxidase. Large overdoses of disulfiram (without ethanol) can cause choreoathetosis, a Parkinson-like syndrome and endocrine abnormalities as well as hallucinations and in severe cases coma and death from cardiovascular collapse. Many authors believe that carbon disulfide is responsible for these evil effects from a large disulfiram overdose.

Finally, there is the problem of disulfiram overdose in a child. Is this a different syndrome than when an adult overdoses on the drug? To begin with, is this really a problem? Well, many alcoholic patients have children, many alcoholics are unemployed, have marital discord, have unstable life styles, and many alcoholics are on chronic disulfiram therapy; this adds up to a great potential for accidental ingestion of this drug by members of the preschool population. Disulfiram overdose in a child is different than in adults and according to the literature has generally a poor prognosis. Overdose of this drug by a child, after a lag time of as long as 12 hours, causes *vomiting, lethargy, hypotonia* which can progress to stupor or *coma* (sounds a bit like Reye's syndrome, doesn't it? However, ammonia and transaminase levels are normal). There is frequently in association with the foregoing: *dehydration,* pronounced *tachypnea* and *tachycardia* and *very poor muscle tone;* deep tendon reflexes are typically very decreased often to the point of being absent. *Ketosis* which is typically disproportionate to the degree of dehydration seems to be a fairly consistent laboratory finding. In adults, one sees more of a picture of bizarre thought processes, agitation and hallucinations with disulfiram overdose. On the other hand *stupor, weakness, hypotonia* and *coma* are rare in adults but almost the rule in *children.*

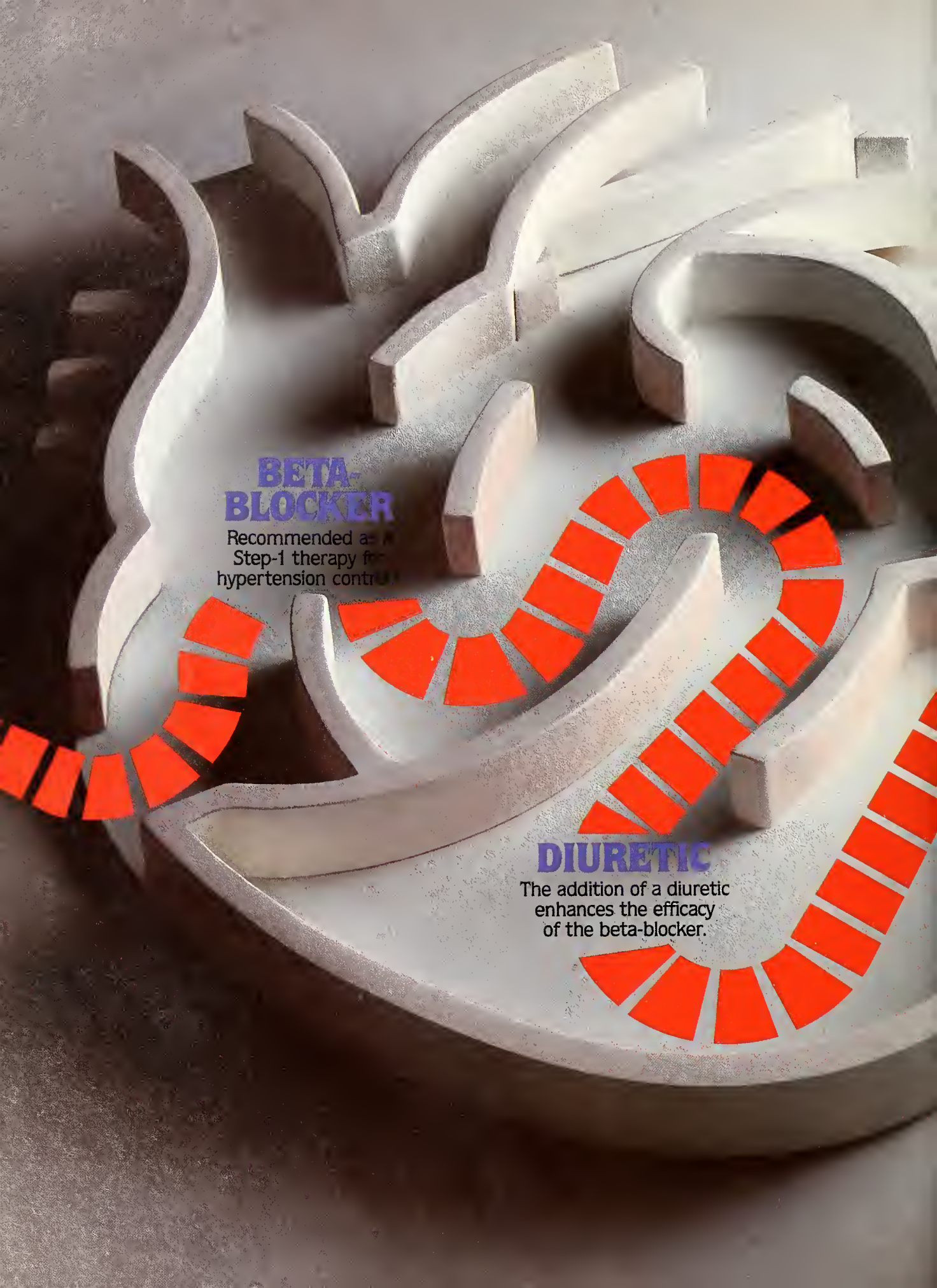
Without a very precise history, especially about the presence of alcoholics in the family who might be taking Antabuse, this is a difficult diagnosis to make. Disulfiram is not detected by the usual "toxic screen." To confirm an overdose you need to obtain levels for disulfiram or its metabolites: diethylthiocarbonate and diethylamine and carbon disulfide. Needless to say, these levels are not available at most hospitals. Still another problem related to these levels is the fact that disulfiram is rapidly reduced in the patient and may be undetectable in serum soon after ingestion. The level of disulfiram or its metabolites does not correlate with the severity of intoxication anyway so don't feel badly if you cannot get them. Do what a good clinician always does: be a skillful data collector.

The treatment of disulfiram intoxication is not very thrilling and is mainly supportive; even elements of this supportive management involve controversy. For example, although gastric emptying is recommended early on, some authorities advise against the use of ipecac syrup because this product contains ethanol and could potentially precipitate an ethanol-disulfiram reaction. Gastric lavage would seem to be a safer choice. Although the standard gastrointestinal decontamination procedures of administering activated charcoal and cathartics are recommended, there are no good data that prove they make a difference. Some authors recommend the intravenous use of pyridoxine (as in INH overdose) if signs of neurological toxicity are present. The rapid absorption and high lipophilic potential of disulfiram make extracorporeal removal such as charcoal hemoperfusion, etc. an unlikely solution to the problem. Very clearly there is no antidote and you must treat the patient and not the toxin. An overdose of disulfiram in a young child can be devastating — the result could be severe brain damage or death.

I have often wondered what kind of a writer F. Scott Fitzgerald would have been if he had been a member of AA or had been on chronic disulfiram therapy. I hate to say this, but I would guess in his case art imitated life and he would probably have failed as a man of letters without his "dark nights of the soul." For myself, iced tea or a glass of soda-pop seems to make a difference and this probably explains why I never make the *New York Times* best seller lists.

The Logical Path to Compliance




BETA-
BLOCKER
Recommended a-
Step-1 therapy fr
hypertension contr
DIURETIC
The addition of a diuretic
enhances the efficacy
of the beta-blocker.

IN HYPERTENSION END POINT:

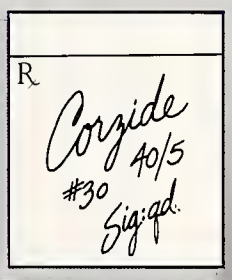
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When hypertension control is complicated by the need for a beta-blocker plus a thiazide, CORZIDE® simplifies patient compliance with reliable once-a-day dosing in a single tablet.

CORZIDE®

(nadolol-bendroflumethiazide tablets)

Makes good sense



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Innovators in cardiovascular medicine

*Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984.

Please see brief summary of prescribing information on following page

CORZIDE®

(nadolol-bendroflumethiazide tablets)

CORZIDE® 40/5
CORZIDE® 80/5
Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents: CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

Exacerbation of Ischamic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — Nadolol — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide,* and PRECAUTIONS, *General, Bendroflumethiazide).*

Drug Interactions — Nadolol — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents: **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery).* **Antidiabetic drugs (oral agents and insulin)** — hyperglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol, Diabetes* and *Hypoglycemia).* **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenargic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated; adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxents, nondepolarizing (a.g., tubocurarina)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide).*

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — Teratogenic Effects — Nadolol — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus; these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss; emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allargic** — fever combined with aching and sore throat, laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash, arterial insufficiency.

Bandroflumethiazide — Gastrointestinal System — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersansitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Othar** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a β_2-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

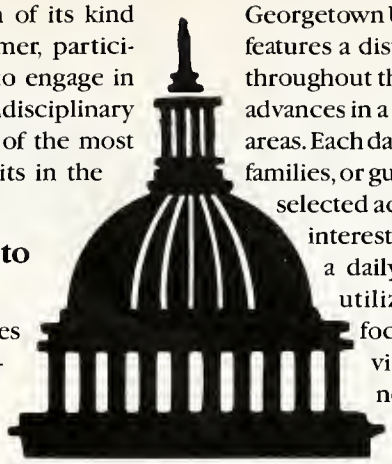
DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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505-502 Issued: March 1985

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AFTER BREAKTHROUGH BLEEDING AND AMENORRHEA...
SHE'S ABOUT TO GIVE UP ON ORAL CONTRACEPTION.
NORLESTRIN®
(1 mg norethindrone acetate and 50 mcg ethinyl estradiol tablets, USP)
150
BECAUSE SOMETIMES A 50 IS PREFERABLE

Brief Summary of Prescribing Information
NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information. A Brief Summary follows

DESCRIPTION
Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years; in clinical trials with Norlestrin 2.5/50 involving 96,388 cycles, there was a pregnancy rate of 0.22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See WARNING No. 5)
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved.

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives, however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy. Birth Defects in Offspring, and Malignancy in Female Offspring.* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected.

(a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis; pulmonary embolism; coronary thrombosis, cerebral thrombosis, cerebral hemorrhage; hypertension; gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis; neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma, breast changes, change in weight, change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature, intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme; erythema nodosum; hemorrhagic eruption, vaginitis, porphyria.

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Norlestrin 21 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin 21 2.5/50 is available in compacts each containing 21 tablets. Each tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin Fe 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin FE 2.5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin 28 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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North Carolina Medical Journal

Features for Patients

May 1985

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Debbie Lechner, L.P.T.
Updated 1985 by Donald McCollum, M.D.

My long term friend and neighbor, Mrs. Alice Cleland, became a candidate far hip surgery. I wheeled her to her room and noticed that she was holding a booklet telling her what to expect. She said that this was the single most helpful piece of paper ever given to her by a doctor. We are publishing the document. I hope it will inspire each of our readers to feed us information that is useful in patient care. All of you have useful tricks up your sleeves. The *Journal* is a good medium far sharing them with your colleagues.

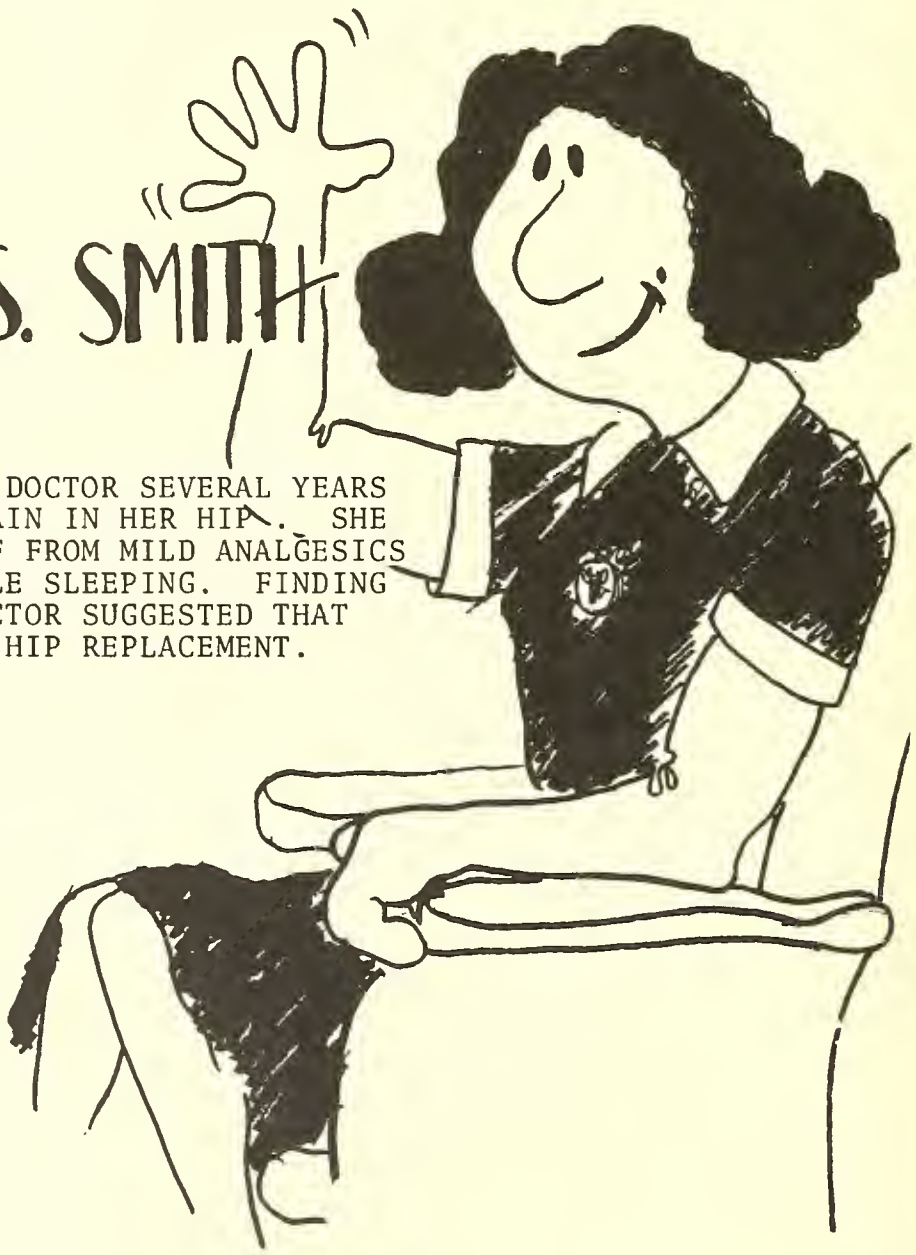
E.A.S.



SO YOU ARE GOING TO HAVE A TOTAL HIP REPLACEMENT...

THIS BOOKLET IS PROVIDED TO HELP ANSWER SOME QUESTIONS YOU MIGHT HAVE ABOUT YOUR SURGERY AND TO GIVE YOU THE INFORMATION WHICH YOU'LL NEED TO MAKE THE QUICKEST POSSIBLE RECOVERY.

MEET MRS. SMITH

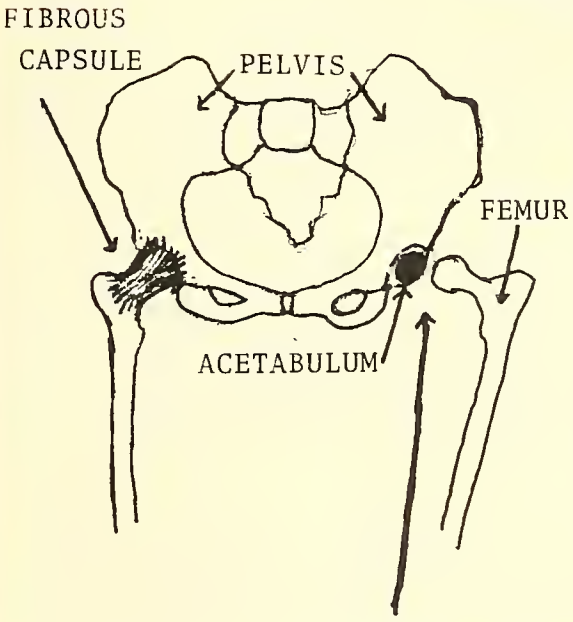


SHE BEGAN SEEING HER DOCTOR SEVERAL YEARS AGO FOR INCREASING PAIN IN HER HIP. SHE WAS GETTING NO RELIEF FROM MILD ANALGESICS AND WAS HAVING TROUBLE SLEEPING. FINDING NO INFECTION, HER DOCTOR SUGGESTED THAT SHE CONSIDER A TOTAL HIP REPLACEMENT.

A TOTAL HIP REPLACEMENT IS AN OPERATION WHERE THE DISEASED HIP JOINT IS REMOVED AND REPLACED BY AN ARTIFICIAL ONE.



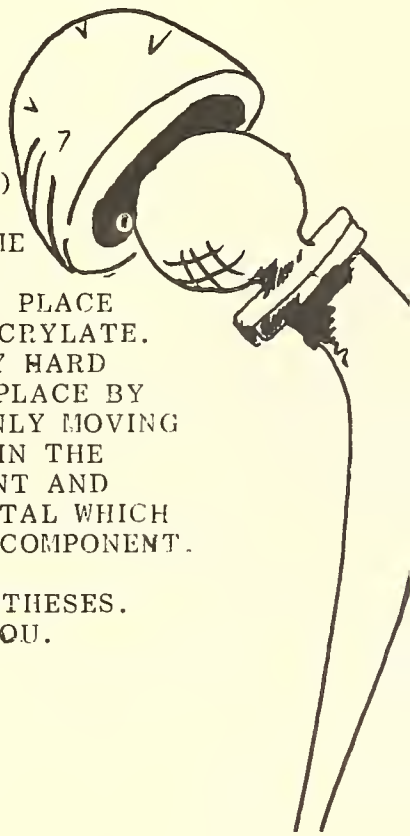
GEE, I DON'T KNOW ANYTHING...



HIP JOINT (OPENED)

THE NORMAL HUMAN HIP IS A "BALL AND SOCKET" JOINT. THE "BALL" IS THE HEAD OF THE FEMUR (THE LONG BONE OF THE THIGH), AND THE "SOCKET" IS A CUP-SHAPED AREA OF THE PELVIS CALLED THE ACETABULUM. THE INSIDE OF THE ACETABULUM AND THE HEAD OF THE FEMUR ARE COVERED WITH A GRISTLE-LIKE CARTILAGE WHICH PROVIDES A CUSHION FOR THE BONES AS WELL AS A SMOOTH, GLIDING SURFACE WHERE THEY MOVE AGAINST EACH OTHER. THE JOINT IS LUBRICATED WITH SYNOVIAL FLUID WHICH IS CONTAINED WITHIN THE JOINT CAPSULE. THE JOINT CAPSULE IS THE OUTER COVERING OF THE JOINT, AND IT IS MADE UP OF TOUGH FIBERS CALLED LIGAMENTS. THESE FIBERS HOLD THE BALL OF THE HIP JOINT IN THE SOCKET. .

ABOUT THE PROSTHESIS



THE ARTIFICIAL JOINT IS CALLED A PROSTHESIS (PROS-TEA'-SIS) AND IT CONSISTS OF TWO PARTS. ONE PART, THE FEMORAL COMPONENT, IS MADE OF METAL AND REPLACES THE HEAD OF THE FEMUR OR "BALL" PART OF THE JOINT. THE LONG STEM FITS INTO THE HOLLOW SHAFT OF THE FEMUR AND IS CEMENTED INTO PLACE BY A SPECIAL ACRYLIC BONDING AGENT CALLED METHYL METHACRYLATE. THE "CUP" PART OF THE PROSTHESIS IS MADE OF AN EXTREMELY HARD PLASTIC CALLED POLYETHYLENE, AND IS ALSO CEMENTED INTO PLACE BY METHYL METHACRYLATE. AFTER THE CEMENT HARDENS, THE ONLY MOVING PART OF THE ARTIFICIAL HIP JOINT IS THE INERT METAL BALL IN THE PLASTIC SOCKET. SEVERAL HIP PROSTHESES DO NOT USE CEMENT AND ARE HELD IN PLACE BY BONY INGROWTH INTO PORES OF THE METAL WHICH COVERS THE CUP AND THE METAL WHICH COVERS THE FEMORAL COMPONENT.

THERE ARE SEVERAL DIFFERENT MODELS AND SIZES OF HIP PROSTHESES. YOUR DOCTOR WILL CHOOSE THE ONE HE THINKS IS BEST FOR YOU.

WHEN DO I GO TO THE HOSPITAL?



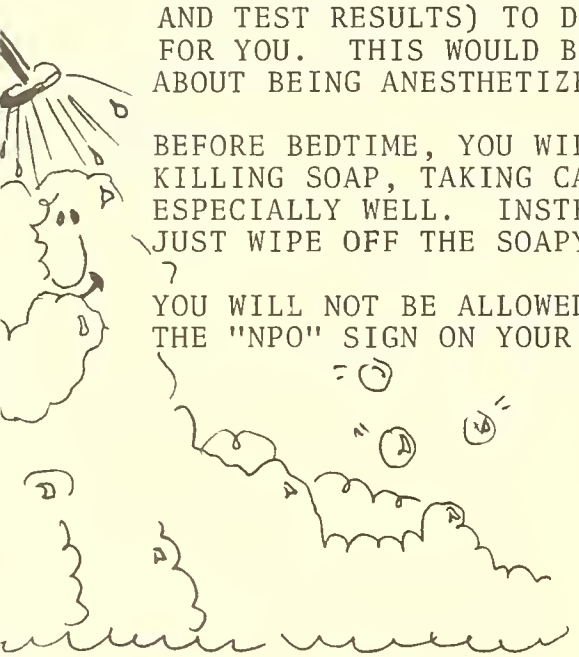
YOU WILL PROBABLY ENTER THE HOSPITAL ONE DAY BEFORE YOUR SURGERY HAS BEEN SCHEDULED TO ALLOW TIME FOR TESTS AND PREPARATION. THIS WILL BE A BUSY TIME. YOUR MEDICAL HISTORY WILL BE TAKEN, AND YOU WILL BE GIVEN A PHYSICAL EXAMINATION. OTHER TESTS WILL EITHER BE DONE IN THE CLINIC OR LATER WHEN YOU ARRIVE IN YOUR ROOM ON THE WARD.



THE NURSE WILL ASK YOU TO PROVIDE A URINE SAMPLE AND EXPLAIN THE PROPER WAY TO OBTAIN THE SPECIMEN. BLOOD SAMPLES WILL BE DRAWN BY A LAB TECHNICIAN, SO THAT IT CAN BE TESTED AND CROSS-MATCHED IN THE BLOOD BANK. SINCE IT ISN'T UNUSUAL FOR A TRANSFUSION TO BE DONE DURING SURGERY, THE DOCTOR LIKES TO HAVE SEVERAL UNITS OF YOUR TYPE OF BLOOD ON HAND. IN ADDITION, A CHEST X-RAY AND AN EKG (ELECTROCARDIOGRAM) WILL BE PERFORMED. MOST OF THESE TESTS WILL BE DONE ON THE DAY OF ADMISSION, BUT IF THE DOCTOR SHOULD ORDER ANY ADDITIONAL ONES, THEY WILL BE MADE THE FOLLOWING DAY. FOR EXAMPLE, DEPENDING UPON YOUR AGE AND GENERAL CONDITION, THE DOCTOR MAY ORDER A CONSULTATION WITH A CARDIOLOGIST TO GATHER FURTHER INFORMATION SO THAT YOU WILL BE RECEIVING VERY PERSONALIZED CARE.

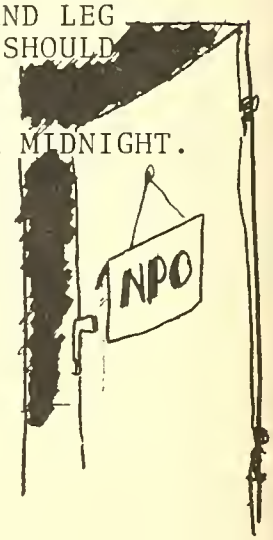
TO MAKE THE TESTING PROCEDURES GO SMOOTHLY, IT IS BEST THAT YOU WEAR A HOSPITAL GOWN AND THAT YOU DO NOT LEAVE THE WARD WITHOUT ASKING THE CHARGE NURSE.

THE DOCTOR WILL WANT TO TALK WITH YOU ABOUT YOUR SURGERY, ANSWER ANY QUESTIONS YOU MIGHT HAVE, AND THEN HAVE YOU SIGN A PERMIT FORM AUTHORIZING THE SURGEON TO PERFORM THE OPERATION. THE ANESTHESIOLOGIST WILL VISIT (AFTER LOOKING AT YOUR CHART AND TEST RESULTS) TO DISCUSS WHICH TYPE OF ANESTHESIA IS BEST FOR YOU. THIS WOULD BE AN IDEAL TIME TO ASK HIM ANY QUESTIONS ABOUT BEING ANESTHETIZED.



BEFORE BEDTIME, YOU WILL NEED TO SHOWER WITH A SPECIAL GERM-KILLING SOAP, TAKING CARE TO SCRUB YOUR HIP, PELVIS, AND LEG ESPECIALLY WELL. INSTEAD OF RINSING OFF THE SOAP YOU SHOULD JUST WIPE OFF THE SOAPY SOLUTION WITH A CLEAN TOWEL.

YOU WILL NOT BE ALLOWED ANYTHING TO EAT OR DRINK AFTER MIDNIGHT. THE "NPO" SIGN ON YOUR DOOR MEANS "NOTHING BY MOUTH."





EARLY THE NEXT MORNING..

EARLY THE NEXT MORNING, THE NURSE WILL WAKE YOU AND ASK YOU TO BATHE AGAIN WITH THE GERM-KILLING SOAP. SOON A NURSE FROM THE OPERATING ROOM WILL COME BY AND SHAVE YOUR LEG AND HIP COMPLETELY. SUCH THOROUGH CLEANSING IS NECESSARY FOR PROTECTING YOU AGAINST INFECTION.

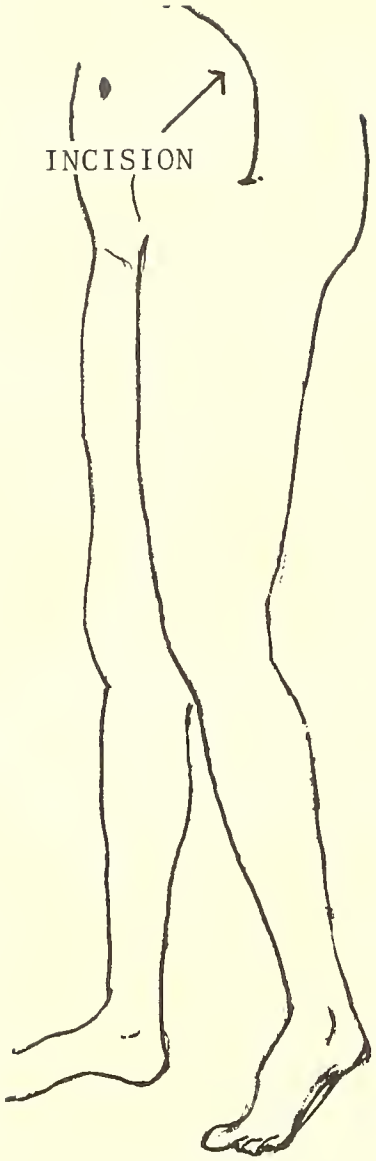
YOU WILL BE GIVEN A HOSPITAL GOWN TO WEAR AND ASKED TO REMOVE ANY OTHER CLOTHES. JEWELRY, MONEY, OR OTHER VALUABLES CAN BE LOCKED UP BY THE NURSE IF YOUR FAMILY CANNOT KEEP THEM FOR YOU. IF YOU WEAR FALSE TEETH, CONTACT LENSES, OR OTHER PROSTHESES, THEY NEED TO BE SAFELY STORED IN YOUR ROOM SO THAT THEY WILL BE PROPERLY CARED FOR AND NOT LOST. NAIL POLISH MUST BE REMOVED SO THAT THE ANESTHESIOLOGIST CAN CHECK YOUR CIRCULATION DURING THE OPERATION.

AM I READY YET?

NOW YOU ARE READY TO BE TAKEN TO THE OPERATING ROOM. THE NURSE WILL HELP YOU TO THE BATHROOM TO EMPTY YOUR BLADDER BEFORE YOU LEAVE. SHE WILL THEN GIVE YOU SOME MEDICINE TO HELP YOU RELAX AND TO DRY UP THE SECRETIONS IN YOUR LUNGS. THIS WILL HELP EASE YOUR BREATHING WHILE YOU ARE ASLEEP, ALTHOUGH IT MAY MAKE YOUR MOUTH FEEL DRY.

A NURSE FROM THE WARD WILL ACCOMPANY YOU AS YOU ARE MOVED IN YOUR OWN BED TO THE ENTRANCE OF THE OPERATING ROOMS. THERE, THE O. R. NURSE WILL CHECK YOU IN BEFORE YOU PROCEED A SHORT DISTANCE TO THE PRE-ANESTHESIA ROOM. YOUR ANESTHETIST WILL MEET YOU TO CHECK YOUR PULSE, BLOOD PRESSURE, AND TO START AN I.V. THE I.V. IS A SMALL TUBE WHICH CARRIES FLUIDS AND MEDICATION INTO A VEIN IN YOUR ARM. AFTER THE I.V. IS IN PLACE, YOU SHOULD SOON FEEL DROWSY AND FALL ASLEEP.





THE OPERATION

THE DOCTOR WILL PROBABLY USE A 7 TO 9 INCH INCISION ALONG THE SIDE OF YOUR HIP. HE WILL THEN LOCATE THE TOUGH CAPSULE OF THE JOINT UNDER THE SURROUNDING MUSCLES. THE CAPSULE IS OPENED, EXPOSING THE INSIDE OF THE JOINT. THE DOCTOR NEXT REMOVES THE HEAD OF THE FEMUR (OR "BALL" PART OF THE JOINT).

NEXT, THE DOCTOR ENLARGES YOUR ACETABULUM ("SOCKET" PART OF THE JOINT) JUST ENOUGH TO HOLD THE ACETABULAR COMPONENT OF THE PROSTHESIS. BOTH COMPONENTS ARE THEN PUT INTO PLACE AND TESTED FOR A PROPER FIT. ONCE THE DOCTOR IS SATISFIED WITH THESE RESULTS, HE CEMENTS BOTH COMPONENTS INTO PLACE AND SUTURES THE WOUND CLOSED. THE OPERATION IS OVER!

THE SURGERY ITSELF TAKES ONLY FROM 1 1/2 TO 3 HOURS, BUT YOUR FAMILY CAN EXPECT YOU TO BE AWAY FROM YOUR ROOM FOR 4 TO 7 HOURS TOTAL. SPECIAL SKIN PREPARATION IN THE OPERATING ROOM TAKES AT LEAST 1/2 HOUR AFTER YOU ARE PUT TO SLEEP! MOST PATIENTS SPEND AT LEAST 2 HOURS IN THE RECOVERY ROOM AFTER SURGERY, BUT IT IS NOT UNUSUAL TO REMAIN THERE FOR AN EVEN LONGER PERIOD OF TIME. YOU WILL BE ABLE TO RETURN TO THE WARD AS SOON AS YOUR DOCTOR FEELS IT IS SAFE TO DO SO.

THE RECOVERY ROOM

YOU WILL BE TAKEN IN YOUR OWN BED TO THE RECOVERY ROOM AFTER SURGERY IS FINISHED. YOU WILL BE PARTIALLY AWAKE BY THIS TIME, BUT YOU WILL STILL FEEL VERY DROWSY. YOUR OWN SPECIAL NURSE WILL STAY WITH YOU AT ALL TIMES, CHECKING YOUR PULSE AND BLOOD PRESSURE FREQUENTLY AS SHE KEEPS CAREFUL WATCH OVER YOUR CONDITION. SHE WILL BE REMINDING YOU TO BREATHE DEEPLY AND TO COUGH SO THAT YOU WILL AWAKEN MORE QUICKLY.



DEEP BREATHING & COUGHING

YOUR LUNGS NORMALLY SECRETE FLUID CONSTANTLY, TO KEEP THE LUNGS MOIST. WHEN YOU ARE IN GOOD HEALTH, THIS CAUSES NO PROBLEMS BECAUSE TINY HAIRS IN YOUR AIRWAYS BRING THE FLUID UP TO THE THROAT AND YOU SWALLOW IT UNCONSCIOUSLY. WHEN YOU ARE PUT TO SLEEP, THE ANESTHESIA SLOWS THE BODY'S MEANS OF BRINGING UP THE FLUID. IF GASSES ARE USED, THEY CAN IRRITATE THE LUNGS SLIGHTLY AND FURTHER INCREASE THE SECRETIONS. THEREFORE, WHEN YOU AWAKEN, THERE IS SOME FLUID IN YOUR LUNGS WHICH WILL REQUIRE COUGHING TO BRING IT UP.

DEEP BREATHING BEFORE COUGHING HELPS TO LOOSEN THIS FLUID AND OPEN UP YOUR LUNGS FOR A GOOD, DEEP COUGH.

YOUR NURSE WILL BE REMINDING YOU OFTEN TO BREATHE DEEPLY AND COUGH!!!

IN ORDER TO DEEP BREATHE AND TO COUGH PROPERLY AFTER SURGERY, IT IS A GOOD IDEA TO PRACTICE THE NIGHT BEFORE.



1. TAKE IN A DEEP BREATH WITH YOUR MOUTH OPEN TO THE COUNT OF 3.

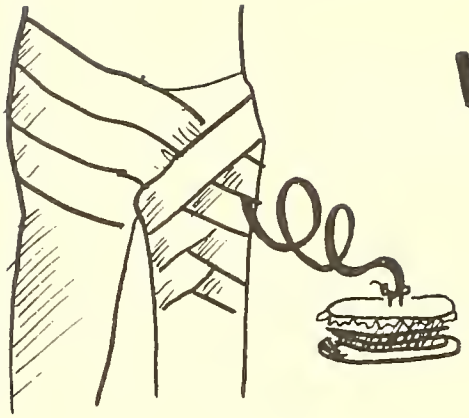
2. PUCKER YOUR LIPS AND BLOW OUT TO THE COUNT OF 6.

3. DO A DEEP DOUBLE COUGH. . ("ahem. . .AHEM")

YOUR ABDOMEN (BELLY AREA) SHOULD MOVE UP AND DOWN WITH EACH DEEP BREATH AND COUGH. THIS ASSURES YOU THAT YOU ARE DOING IT CORRECTLY.

IF THIS FLUID IS NOT COUGHED UP, THE COLLECTION OF FLUID IN YOUR LUNGS COULD CAUSE PNEUMONIA. NOTHING IS MORE EFFECTIVE IN PREVENTING THE ONSET OF PNEUMONIA THAN DEEP BREATHING AND COUGHING.

THIS IS ONE POSITIVE STEP IN SPEEDING YOUR RECOVERY THAT ONLY YOU CAN TAKE!!!



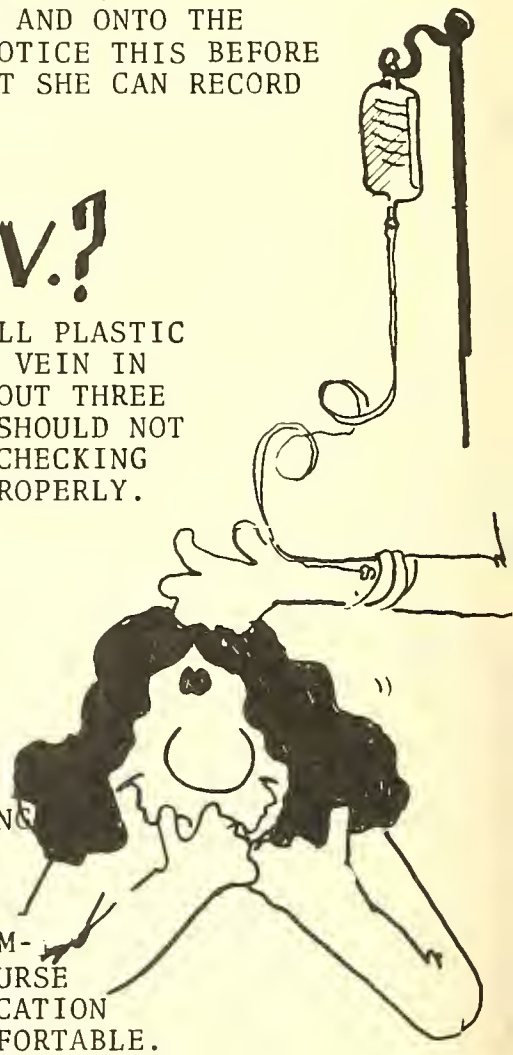
WHAT ABOUT MY HIP?

YOUR HIP WILL BE WRAPPED WITH A SOFT DRESSING WHICH WILL STAY IN PLACE FOR ABOUT FIVE DAYS. AFTER THE DRESSING IS REMOVED, YOUR INCISION WILL BE COVERED WITH A LARGE BANDAID. TEN DAYS AFTER SURGERY WHEN THE WOUND IS HEALED, THE STITCHES OR SKIN CLIPS WILL BE REMOVED.

WHEN YOU AWAKEN FROM SURGERY A PLASTIC TUBING WILL BE NOTICEABLE COMING FROM BENEATH YOUR DRESSING AND ATTACHING TO A SMALL COMPRESSIBLE CONTAINER. THIS IS A DRAIN CALLED A "HEMOVAC" AND IT LEADS TO YOUR INCISION. THE HEMOVAC ALLOWS ANY DRAINAGE IN YOUR WOUND TO RUN OFF AND PREVENTS A PAINFUL SWELLING CALLED A HEMATOMA TO FORM INSIDE YOUR INCISION SITE. THE HEMOVAC WILL BE REMOVED AFTER ALL DRAINAGE HAS STOPPED (ABOUT TWO DAYS). OCCASIONALLY, DRAINAGE WILL SEEP FROM AROUND THE HEMOVAC AND ONTO THE DRESSING. DO NOT BE ALARMED, BUT IF YOU NOTICE THIS BEFORE THE NURSE DOES, BE SURE TO TELL HER SO THAT SHE CAN RECORD THE AMOUNT AND KEEP YOUR DRESSING DRY.

WILL I STILL HAVE AN I.V.?

AS WAS MENTIONED BEFORE, THE I.V. IS A SMALL PLASTIC TUBE THAT CARRIES FLUID AND MEDICINES TO A VEIN IN ONE OF YOUR ARMS. YOU WILL NEED IT FOR ABOUT THREE DAYS TO RECEIVE THESE MEDICATIONS, BUT IT SHOULD NOT CAUSE ANY DISCOMFORT. THE NURSES WILL BE CHECKING IT FREQUENTLY TO MAKE SURE IT IS RUNNING PROPERLY.



WILL THIS BE PAINFUL?

SOME PAIN AND SORENESS IS EXPECTED FOLLOWING HIP SURGERY, BUT YOUR DOCTOR WILL HAVE ORDERED MEDICATION IF YOU SHOULD HAPPEN TO NEED IT. AFTER ABOUT TWO DAYS, REGULAR ASPIRIN SHOULD BE ALL THAT YOU NEED FOR COMFORT. IT IS IMPORTANT THAT YOU TELL THE NURSE AS SOON AS YOU FEEL THE NEED FOR PAIN MEDICATION AND NOT WAIT UNTIL YOU ARE EXTREMELY UNCOMFORTABLE. REMEMBER THAT EVEN THOUGH YOUR NURSE IS CHECKING ON YOU FREQUENTLY, IT IS UP TO YOU TO LET HER KNOW HOW YOU ARE FEELING.

DO I STAY IN BED FOR LONG?

FOR THE FIRST DAY AFTER YOUR SURGERY, YOU WILL NEED TO REMAIN IN BED. ABOUT THE SECOND OR THIRD DAY YOU WILL BE ALLOWED UP IN A CHAIR AND THEN AFTER THAT YOU WILL BEGIN WALKING WITH HELP FROM PHYSICAL THERAPY.

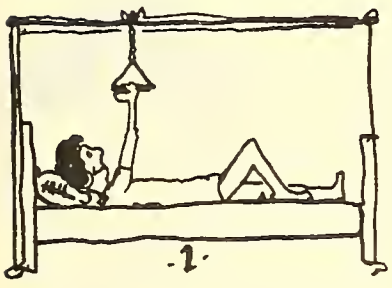
FREQUENT CHANGE OF POSITION HELPS TO CLEAR THE FLUID FROM YOUR LUNGS, IMPROVES YOUR CIRCULATION, AND MAKES YOU MORE COMFORTABLE.



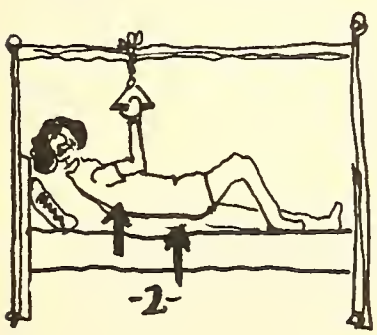
HOW WILL I MOVE?

TO HELP YOU MOVE IN BED AFTER SURGERY, YOUR BED WILL BE EQUIPPED WITH AN OVERHEAD FRAME WHICH SUPPORTS A "TRAPEZE BAR." BY USING YOUR ARMS, YOU CAN MOVE AROUND MORE EASILY. PRACTICING WITH THE TRAPEZE BEFORE SURGERY WILL GIVE YOU THE FEEL OF THE MANEUVER AND WILL BE GOOD PREPARATION FOR USING IT LATER.

IT'S EASY! HERE'S HOW...



IF YOU ARE LYING ON YOUR BACK, JUST BEND YOUR "GOOD" LEG UP KEEPING THE SOLE OF YOUR FOOT FLAT ON THE BED.



REACH UP AND GRAB THE TRAPEZE BAR WITH ONE OR BOTH HANDS.

THEN, BY PULLING ON THE TRAPEZE BAR AND PUSHING DOWN WITH THE LEG THAT IS BENT, YOU CAN LIFT YOUR BODY FROM THE BED AND MOVE IT IN ANY DIRECTION.

WON'T IT BE DANGEROUS TO TURN ON MY HIP?

NO! ACTUALLY, YOUR NEW HIP IS SAFEST WHEN YOU ARE LYING ON IT!!! THIS POSITION AIDS DRAINAGE AND PREVENTS DISLOCATION OF THE JOINT. THE ONLY DANGEROUS POSITION FOR YOU EXISTS WHEN YOU ADDUCT YOUR OPERATIVE LEG. (THAT IS, WHEN YOU MOVE THAT LEG IN TOWARD THE OTHER ONE.) BEFORE YOUR HIP HAS HEALED, IT IS POSSIBLE THAT ADDUCTING YOUR LEG MAY CAUSE DISLOCATION OF THE PROSTHESIS.

BUT REMEMBER...



1. DO NOT ALLOW YOUR OPERATIVE LEG TO SWING INWARD! TRY TO KEEP YOUR LEGS SLIGHTLY APART AT ALL TIMES, PLACING A PILLOW BETWEEN THEM IF NECESSARY.



2. KEEP YOUR FEET AS HIGH AS YOUR KNEES AND HIGHER THAN THE LEVEL OF YOUR HEART WHEN YOU ARE LYING ON YOUR BACK.



3. NEVER CROSS YOUR LEGS.

4. DO NOT TURN ONTO YOUR NON-OPERATIVE SIDE WITHOUT HELP FROM A NURSE. SHE WILL NEED TO SPECIALLY POSITION YOU WITH PILLOWS BEFORE YOU TURN SO THAT DISLOCATION WILL NOT OCCUR.





5. TRY TO KEEP YOUR KNEE CAPS AND TOES POINTED TOWARD THE CEILING WHEN YOU ARE LYING ON YOUR BACK.

BY THE TIME YOU LEAVE THE HOSPITAL, YOU SHOULD BE ABLE TO TURN TO EITHER SIDE SAFELY, BUT YOU SHOULD AVOID CROSSING YOUR LEGS FOR SEVERAL WEEKS.

I'VE HEARD OF BLOOD CLOTS...



BLOOD CLOTS, OR THROMBI, IN THE LEGS ARE A DANGER TO EVERY PATIENT AFTER SURGERY. IF A CLOT SHOULD HAPPEN TO FORM IN THE LEGS, IT COULD BREAK LOOSE AND TRAVEL TO THE LUNGS, CAUSING SERIOUS ILLNESS. ALTHOUGH THIS RARELY OCCURS, EVERY PRECAUTION IS TAKEN TO PREVENT CLOTS FROM FORMING. PART OF YOUR MEDICATION AFTER SURGERY WILL "THIN" YOUR BLOOD SLIGHTLY TO PREVENT CLOT FORMATION. YOU WILL BE GIVEN SPECIAL STOCKINGS TO WEAR AFTER SURGERY AND ASKED TO KEEP YOUR FEET HIGHER THAN HEART LEVEL WHILE LYING IN BED. MOST IMPORTANT, YOU WILL BE DOING SOME EXERCISES TO KEEP YOUR BLOOD CIRCULATING SO THAT CLOTS DON'T HAVE THE CHANCE TO FORM.

DID YOU SAY EXERCISES?

EXERCISING IS VERY IMPORTANT AFTER SURGERY. IT IS A MUST FOR MAINTAINING GOOD CIRCUALTION AND MUSCLE TONE IN YOUR LEGS AND ARMS.

THE FOLLOWING EXERCISES MAY BE BEGUN BEFORE SURGERY. AFTER SURGERY, THEY SHOULD BE DONE AT LEAST FIVE TIMES DURING EACH HOUR THAT YOU ARE AWAKE, UNLESS YOU ARE GIVEN DIFFERENT INSTRUCTIONS.
HOLD EACH OF THE FOLLOWING FOR A SLOW COUNT OF FIVE.

1. CURL AND WIGGLE TOES.
2. MOVE ANKLES UP AND DOWN AND AROUND IN CIRCLES.
3. TIGHTEN KNEES BY STIFFENING YOUR FRONT THIGH MUSCLES.
4. TIGHTEN THE BUTTOCKS MUSCLES WITH KNEES KEPT STRAIGHT.
5. TAKE A DEEP BREATH, FILLING THE LUNGS, THEN LET AIR OUT SLOWLY. COUGH DEEPLY.
6. USING TRAPEZE BAR AND NON-OPERATIVE LEG, LIFT YOUR TRUNK OFF THE BED KEEPING YOUR HIPS STRAIGHT. (DO THIS WHILE LYING ON YOUR BACK.)

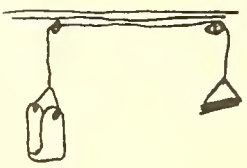
YOUR DOCTORS MAY FEEL THAT YOU SHOULD BEGIN EXERCISES (NUMBERS 1 THROUGH 4) SEVERAL WEEKS BEFORE SURGERY. YOUR MUSCLES WILL BE STRENGTHENED SO THAT YOU WILL ARRIVE FOR SURGERY IN THE BEST POSSIBLE CONDITION AND INCREASE THE SPEED AND EASE OF YOUR RECOVERY.



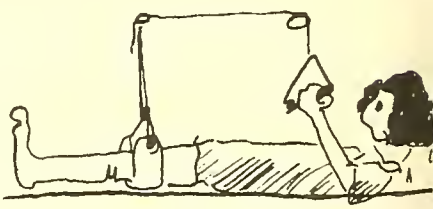
IS THIS THE PHYSICAL THERAPIST?

THE PHYSICAL THERAPIST WILL HELP YOU WITH YOUR MORE ADVANCED EXERCISES AFTER SURGERY. THEY ARE USUALLY BEGUN ON THE FOURTH OR FIFTH DAY FOLLOWING THE OPERATION.

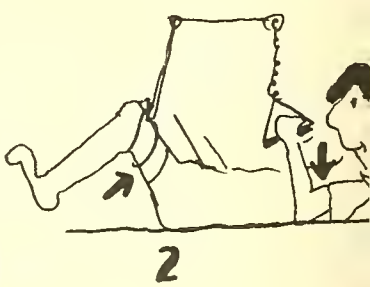
IN ADDITION TO YOUR TRAPEZE BAR, A SLING IS SUSPENDED FROM THE FRAME OVER YOUR BED BY A SYSTEM OF PULLEYS. THE FOLLOWING EXERCISES USING THE SLING WILL BE STARTED 4-5 DAYS AFTER YOUR SURGERY WITH HELP FROM YOUR PHYSICAL THERAPIST. THEY ARE TO BE DONE USING YOUR LEG MUSCLES AS MUCH AS POSSIBLE. YOU SHOULD RELY ON THE USE OF THE SLING ONLY WHEN ABSOLUTELY NECESSARY. BEGIN BY DOING THE NUMBER OF EXERCISES AS YOU ARE INSTRUCTED AND ADD 1 REPETITION EACH TIME YOU DO THEM.



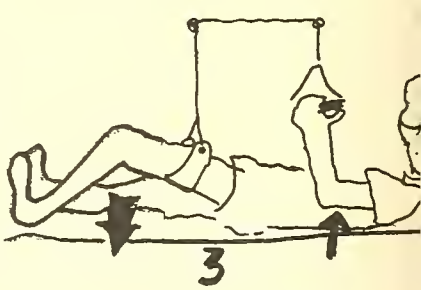
KNEE TO CHEST



1. LIE ON YOUR BACK WITH YOUR LEGS OUT STRAIGHT. PLACE THE PULLEY PAD UNDER YOUR THIGH.



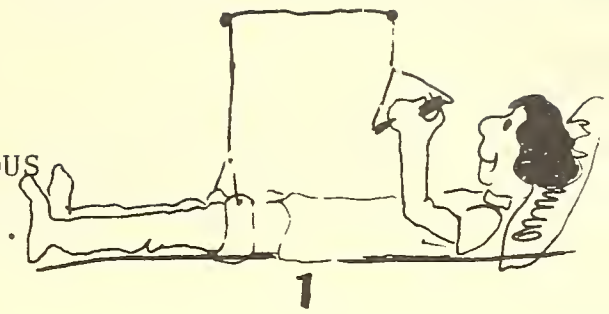
2. BEND YOUR KNEE, RAISING IT UP TOWARD YOUR CHEST. RAISE IT AS FAR AS YOU CAN WITHOUT USING THE PULLEY. THEN, BY PULLING STRAIGHT DOWN ON THE PULLEY, YOU CAN RAISE YOUR LEG FURTHER UP TOWARD YOUR CHEST. YOU WILL HAVE TO WORK THROUGH SOME PAIN, BUT DO NOT FORCE YOUR LEG BEYOND REASON.



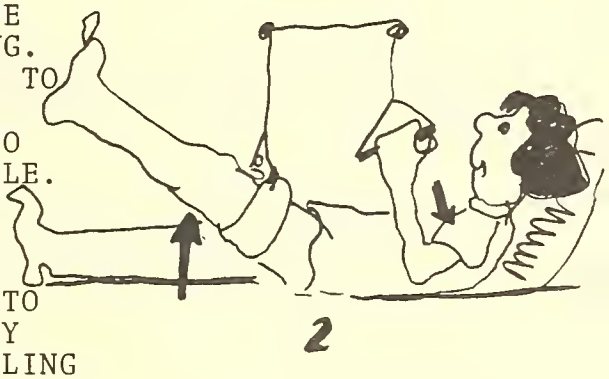
3. THEN LOWER YOUR LEG BACK TO THE STARTING POSITION #1 BY STRAIGHTENING YOUR KNEE AND RELEASING THE PULLEY GRADUALLY.

STRAIGHT LEG

1. BEGIN IN SAME POSITION AS PREVIOUS EXERCISE---ON YOUR BACK, LEGS STRAIGHT, PULLEY PAD UNDER THIGH.



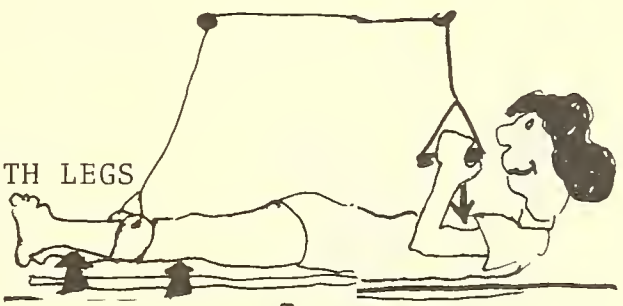
2. KEEPING YOUR KNEE STRAIGHT, RAISE YOUR ENTIRE LEG UP TOWARD CEILING. YOU WILL PROBABLY NEED THE SLING TO HELP YOU, BUT YOU SHOULD CONCENTRATE ON USING THE LEG MUSCLES TO RAISE YOUR LEG AS MUCH AS POSSIBLE.



3. THEN SLOWLY LOWER YOUR LEG BACK TO STARTING POSITION #1 BY GRADUALLY RELEASING THE PULLEY AND CONTROLLING YOUR LEG AS IT GOES BACK DOWN.

LEG TO SIDE

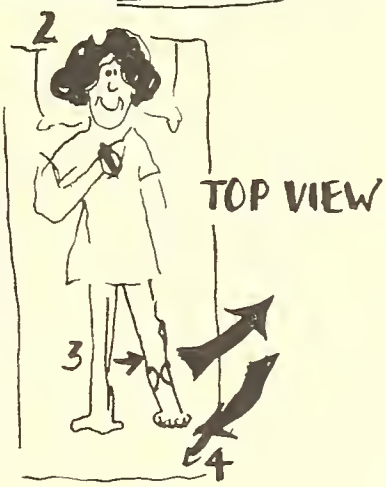
1. LIE ON YOUR BACK AS BEFORE WITH LEGS STRAIGHT AND SLING UNDER YOUR CALF.



2. KEEPING YOUR KNEE STRAIGHT, PULL DOWN ON PULLEY HANDLE LIFTING YOUR LEG UP JUST ENOUGH FOR THE HEEL TO BARELY CLEAR THE BED---NO FURTHER!

3. THEN MOVE YOUR LEG OUT TO THE SIDE, KEEPING YOUR KNEE STRAIGHT AND POINTING UP TOWARD THE CEILING.

4. THEN BRING LEG BACK IN TOWARD THE CENTER.

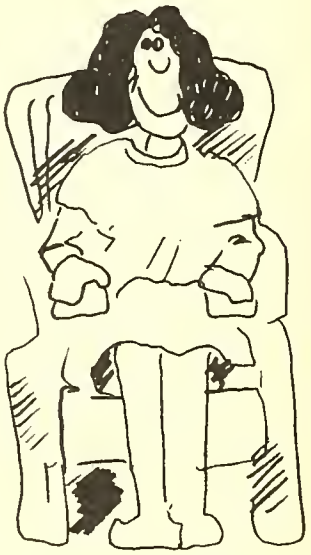


WHEW! SOUNDS TIRING! WHY SHOULD I?

THE BENEFITS THAT YOU RECEIVE FROM YOUR NEW HIP JOINT WILL DEPEND LARGELY ON YOU! YOU MUST EXERCISE FAITHFULLY AND CORRECTLY, FOLLOWING INSTRUCTIONS FROM YOUR DOCTOR AND THERAPIST TO THE LETTER! AT THIS POINT YOU BECOME THE KEY TO A SUCCESSFUL RECOVERY AND A HAPPY LIFE WITH YOUR NEW HIP.

WHEN CAN I BE OUT OF BED?

MANY PATIENTS ARE ABLE TO BE OUT OF BED IN A CHAIR FOR SHORT PERIODS OF TIME AS EARLY AS THE SECOND OR THIRD DAY.



CAN I WALK AGAIN SOON?



BY THE FIFTH DAY OR SO, YOU WILL PROBABLY BEGIN WALKING WITH HELP FROM THE PHYSICAL THERAPY DEPARTMENT. SINCE YOU WILL NEED TO USE A WALKER OR CRUTCHES FOR SOME TIME AT HOME, IT IS IMPORTANT TO LEARN TO USE THEM WELL WHILE YOU ARE IN THE HOSPITAL.

PAY STRICT ATTENTION TO THE THERAPIST'S INSTRUCTIONS AND TAKE CARE NOT TO PLACE ANY MORE WEIGHT ON YOUR NEW HIP THAN YOU ARE INSTRUCTED.

DO I TAKE SPECIAL CARE AT HOME?

WITHIN A FEW MONTHS AFTER YOU LEAVE THE HOSPITAL, YOU SHOULD BE REGAINING FULL USE OF YOUR NEW HIP. GENERALLY, IF YOU ARE TAKING GOOD CARE OF YOURSELF, YOUR HIP WILL NOT REQUIRE ANY SPECIAL ATTENTION.

ANY PRECAUTIONS?



THE ONLY REAL PRECAUTION YOU WILL NEED TO TAKE CONCERNS INFECTIONS. BACTERIA WHICH NORMALLY CAUSE NO PROBLEMS IN YOUR BODY SOMETIMES DO CAUSE PROBLEMS IN A NEW HIP BECAUSE THERE IS NO BLOOD SUPPLY IN THE ARTIFICIAL JOINT TO FIGHT BACTERIA.

THEREFORE, IF YOU ARE TO BE TREATED BY ANY OTHER DOCTORS OR DENTISTS, IT IS IMPORTANT TO INFORM THEM ABOUT YOUR HIP, IN CASE IT WOULD BE NECESSARY FOR THEM TO PROTECT YOU WITH ANTIBIOTICS.

AFTER ANY SURGERY THE MOUTH OR RECTUM REQUIRES SPECIAL CAUTION. IF YOU HAVE YOUR TEETH CLEANED AND SCALED, YOU SHOULD TAKE ANTIBIOTICS ONE HOUR BEFORE AND SIX HOURS AFTER THE PROCEDURE.

AND. . . IF YOU SHOULD NOTICE ANY EXCESSIVE PAIN, SWELLING OR REDNESS IN YOUR HIP JOINT,

CALL HIM IMMEDIATELY!



BY EXPRESSING HER NEEDS AND CONCERNS WITH THE HEALTH CARE TEAM AND CAREFULLY FOLLOWING THEIR INSTRUCTIONS, MRS. SMITH EXPERIENCED A RAPID RECOVERY FROM SURGERY. SHE HAS NOW RETURNED TO HER PREVIOUS ACTIVITIES AND IS ENJOYING LIFE WITH HER TOTAL HIP REPLACEMENT!

HER CONVERSATIONS WITH THE SURGEON, THE NURSES, AND THERAPIST ANSWERED ALL OF HER QUESTIONS AND PERHAPS SEVERAL OF YOURS.



BY WORKING TOGETHER, WE CAN BEST ACHIEVE OUR GOALS FOR YOU. . . A SPEEDY RECOVERY AND MANY HAPPY YEARS WITH YOUR

TOTAL HIP REPLACEMENT!

Angina comes in many forms...

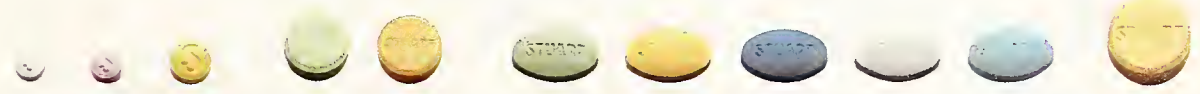


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SORBITRATE®

(ISOSORBIDE DINITRATE)

Unsurpassed flexibility in nitrate therapy.



2.5 mg 5 mg 10 mg
Sublingual Tablets

5 mg 10 mg
Chewable Tablets

5 mg 10 mg 20 mg 30 mg 40 mg
Oral "Swallow" Tablets

40 mg
Sustained Action "Swallow" Tablets

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See following page for brief summary of prescribing information.

SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycenn.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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THE LIFE AND WRITINGS OF JOHN WESLEY LONG, M.D., 1859-1926

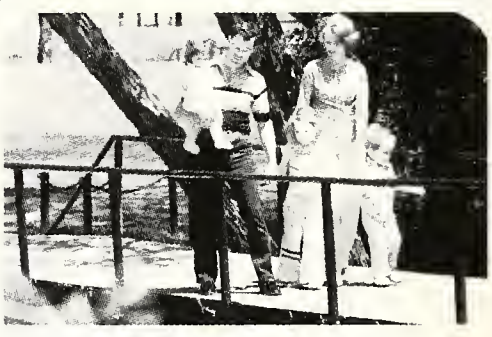
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AIR FORCE
A great way of life

Dr. Joseph Willis Beard: A Mighty Man, 1902-1983

R. McIntyre Bridges, M.D.

FEW men have been so much to so many in so short a period of time. Dr. Beard's accomplishments as a pioneer virologist, a teaching surgeon, a dairy farmer, a philosopher and an admired genius will stand the test of time.

Joseph Willis Beard was born in Athens, Louisiana, in 1902, the eldest of two sons of Jasper Beard and Frazier Bridges. To know and understand the obsessive drive of this man requires that one know his early background and childhood. We must spend the time on Dr. Beard's parents in order to fully appreciate his desire to develop character and intellect, though these characteristics are poles apart. Intellect sufficeth not; character is also needed.

His father, Jasper, was a humble hardwood floor finisher. All of his work was by hand and on his knees. Sanding and varnishing hardwood floors produced knees of enormous size. To have seen them, one would have expressed amazement at his ability to work. Jasper's role was vital to the making of Joe Beard, since he saved with an obsession to educate Joe. Ida Bridges Hall, his wife's sister, found six thousand dollars in a coffee can; Jasper told her, "This is for Joe's education, and I will do all in my power to see that he is educated."

His mother, Frazier Beard, was the oldest of five sisters and two brothers, children of the Sophie and Wardlow Bridges family (figure 1). Like her mother, Sophie, Frazier assumed a matriarchal and domineering stance, which prohibited any emotional closeness.

To provide some insight into the Bridges girls, Hunter Bridges, oldest son of Sophie and Wardlow Bridges, bought a set of the Harvard Classics. Frazier's sisters saw them, declared them pornographic, and burned the set in the back yard!

No one ever doubted the courage of Joe Beard. As a child he was independent, and he would accept any physical challenge. At the age of thirteen he was forced to leave his home in Athens, Louisiana because of his inability to socialize with his peers. He was sent to Shreveport, Louisiana to live with his mother's family, the Bridges, who had moved to Shreveport in 1910. A drought had forced them to move to Travis Street across from Shreve Memorial Library.

Wardlow Bridges, his grandfather, had been a school teacher in Athens, Louisiana. Upon moving to Shreveport

From 128 Homer Road, Minden, LA 71055-2799.



Figure 1. *Joe Beard as a baby sitting on his mother's lap in a photograph of the Bridges family.*

he became a night watchman at warehouses on the banks of the Red River. Each night Joe Beard would go to work with his grandfather, who taught him to read and who instilled in him the desire to learn. Having built-in courage, he now developed an intense desire for knowledge. These two traits he always considered the requirements for greatness.

A year and a half with the Bridges family ended because Joe Beard was unable to get along with the Bridges' youngest son, Murphy, and he was again forced to move. His parents moved from Athens to Shreveport and Joe registered at the Hope Street High School, across from the library, but found little success there. He spent his days in the Shreve Memorial Library. The librarian would pile books on his desk in the library and Joe became obsessed with the wisdom of Plato, Aristotle, Shakespeare and others. Yet he never graduated from high school.

At fifteen years of age a tragedy struck that left its scar on Joe for life. One day a friend and Joe went hunting. His mother insisted that Joe take his younger brother, Ross, along. At Seven Springs, a wooded area in Shreveport, the friend pointed his gun at Ross, which he thought was unloaded, trying to discourage his following them. A shotgun shell happened to be in the gun and, when triggered, exploded. Ross died five months later. Joe's mother, never expressing much love, blamed Joe, and provided him a life of misery after the death of Ross. At this point in Joe's life one must ask the question, "Did this motherly rejection contribute to his greatness?" His quest for knowledge through books became his world.

At the age of seventeen Joe divorced himself from his family and went to work clearing rights-of-way for roads and railroads around Shreveport. He fed his thirst for knowledge by reading anything he could obtain.

After three years on road gangs he presented himself to Centenary College, a private Methodist School in Shreveport, Louisiana. With no High School diploma, he talked his way past the admissions office. He obviously excelled. In 1922, he entered the University of Chicago. He graduated with a Bachelor of Science degree (figure 2), and applied and was accepted for medical school at Vanderbilt University. Shortly after entering Medical School he married Louise Conley, a fellow medical student. After obtaining his M.D. degree he interned and began his surgical residency. Two years into his surgical residency his first marriage ended in divorce.

Shortly afterward he married a nurse at Vanderbilt Hospital, Dorothy Waters (figure 3). This marriage was to endure to his death. Dorothy Beard's interests were inseparable from Dr. Joe Beard's interests and they worked together diligently.

At Vanderbilt, Al Blalock, a classmate, was a good friend of Dr. Beard. Dr. Beard had an ability to seek out those of intellect and attracted the same. Dr. Blalock became Department Head & Chief of Surgery at Johns Hopkins University Medical School.

One should clarify friendships of Dr. Joseph W. Beard: he avoided familiarities in relations with others. He was critical with a vengeance of those superficial with knowledge and of the ignorant who had the opportunity to be otherwise. As he once said, "The stars keep their brilliance by not making themselves common." One would derive



Figure 2. *Dr. Beard's graduation picture from the University of Chicago.*



Figure 3. *Dorothy Beard as a surgical nurse at Vanderbilt University Medical School.*

the impression that Joe Beard felt familiarity bordered on vulgarity. However, one knowing his childhood would gain the impression he feared being hurt.

While in his surgical residency he became interested in the brand new field of viral research and, finishing his residency, he went to Rockefeller Center to work with Peyton Rouse. Peyton Rouse was Dr. Beard's ruling star — as Joe Beard would say, "None so helpless as not to have one." Peyton Rouse and Dr. Beard were pioneers in viral research and attracted many men to the field.

In 1937, Joe joined the faculty of Duke University Medical School as a professor of experimental surgery and viral research (figure 4). In the words of Dr. Eugene Stead, Professor of Medicine and Head of the Department of Medicine, no other member of the faculty had more to do with changing Duke University Medical School from a regional institution to one of national and international recognition. His productivity as a viral scientist escalated through the years at Duke University Medical School.

Shortly after Dr. Beard joined the University staff, the survival of the whole thoroughbred horse population in Kentucky was threatened by equine encephalitis. With a grant from Lederle Laboratories, Dr. Beard developed a vaccine which prevented the death of thousands of horses nationwide. This outstanding achievement was to end in a personal tragedy.

At the insistence of representatives of Lederle Laboratories Dr. Beard patented the vaccine. His work resulted in the first successful vaccine effective against the virus of equine encephalitis. The discovery attracted national and international attention. Rumors were circulated that he was being considered for the Nobel Prize. When the existence of a patent was disclosed, even though all proceeds were designated for the Dorothy Beard Research Fund, his name was withdrawn. As Dr. Beard related to me, "McIntyre, find your proper place by merit, not by presumption. Integrity alone is not sufficient, push and insistence is degrading. Things arrived at by this means are sprinkled with dust that discredit and destroy reputations. The true way is the middle one, halfway between deserving a place and the other way, luck."



Figure 4. *Dorothy Beard working in the Bell Building virus research laboratory in 1956.*

The creation of a red brick building devoted to viral research and a teaching laboratory for dog surgery was an architectural landmark for Duke University. It was the first non-Gothic architecture on the Duke University campus. The name Bell Building was given in honor of the financier. Needless to say it was to remain a monument at the University. The research part of the building was named The Dorothy and Joe Beard Research Laboratory several years prior to their deaths. One must question whether the modernistic hospital now standing there would have ever been built if the architectural deviation was not first initiated by Dr. Beard. A multitude of viral research papers have emerged from the brick building. But the single largest contribution was producing men in the field of viral research world-wide which reads like "Who's Who" in medical research.

Another contribution goes unnoticed. How many lives were saved during World War II by his institution of a course in "Dog Surgery"? He was a dynamic teacher and insisted on sterile technique, a square knot, and the survival of the dog after ten different operations. These procedures left a lasting impression on uncounted students. Many medical students entered World War II with his being the only surgical instruction they received. The number of surgeons today influenced by his techniques is legion. His greatest asset was the ability to sense men's moods and adapt himself to each, genial or serious as the case may be. Dr. Beard was considered by all students to be unrelenting in perfection and uncompromising in discipline. Much to the amazement of outsiders, he was presented "Most Distinguished Teacher Award" by the Duke Alumni Association several years ago.

In this medical history of Dr. Joseph Willis Beard I must deviate to include my relationship. This I feel provides more insight than can be provided by anyone else.

A graduate of Louisiana State University in 1945, I was invited to Duke University Medical School for a medical school interview. After a standup bus ride from Baton Rouge, Louisiana to Durham, North Carolina I arrived after thirty-six hours of travel in nothing short of a disastrous condition. Joe and Dorothy Beard were there to meet me. He appeared seven feet tall, with bushy eyebrows, and mean looking on my first meeting with him (figure 5).

My efforts to gain admission were in vain. My inclination was to give up. After two days in Durham, a series of letters was exchanged between Joe and me. Failure was not a word in Dr. Beard's vocabulary. In answer to a letter I had



Figure 5. *Dr. Beard in 1945 when I first met him.*

written, Joe wrote, "You yourself said that if you didn't do well during your present semester you felt you ought not to go on. This would be a mistake, for it will be much simpler to take a new lease on life in new surroundings. Let's not give up the proposition. You said you wanted to study medicine, so let's go ahead and do it now and have no talk of quitting until you have definitely failed out." This is just an example of the encouragement Joe Beard gave. That was in June 1945.

In October 1945, I returned to Duke University as a graduate student and enrolled in Biochemistry, Statistics, and Scientific German. Scientific German was nothing short of challenging. With only two quarters of German at Louisiana State University, I was most inadequate in classroom activity. At this time Dr. Beard was in bed at his farm home recuperating from tuberculosis. He talked with the German Professor and obtained permission for me to drop from classroom activity and take the final examination for my grade. He explained to the teacher that he would teach me Scientific German.

For four months each Friday at five o'clock, Dorothy Beard drove me to the Beard farm. Dr. Beard taught me Scientific German from 6:00 p.m. to 11:00 p.m. on Fridays; from 8:00 a.m. to 11:00 p.m. on Saturdays, and from 8:00 a.m. to 5:00 p.m. on Sundays. Much to Dr. Beard's delight I took the Scientific German examination and received a B in the course, with As in Statistics and Biochemistry.

This four months of association with Dr. Beard was most enlightening. His conversations were punctuated with "hell" and "damn." He used the words for emphasis as no other person I have known. Their use was unnoticed in his speech and one came to expect them for reinforcement. This habit arose unquestionably in his childhood, working with road gangs and growing up in the Queensboro section of Shreveport, Louisiana. This area was the other side of the tracks, and demanded a tough personality. Having grown up in the same environment, I know toughness in talk and actions was a necessity. Fighting was commonplace and intellectual behavior was unacceptable among one's peers.

I felt if I continued at Duke the next semester I would have been admitted to Medical School. However, there was a war going on, and I could not wait to get an inguinal hernia repaired and enlist in the army. The impression Joe Beard left on a young nineteen-year-old graduate of L.S.U. was immeasurable.

Following my leaving Duke, correspondence was continued between Joe and me. The interesting phenomenon was that each letter was answered and a copy of the letter I had written was sent back with corrections of English and grammar.

In 1947, I was discharged from the Army and entered L.S.U. for a graduate degree in Physiology. On application I was admitted to Duke University Medical School. Dr. Beard and I made a pact that our first-cousin relationship would remain unknown.

In 1949, I entered Duke University Medical School. Dr. Beard and I became very close, a relationship I failed to see with his other acquaintances. Dr. Beard avoided close relationships with anyone (figure 6). An unloving mother,



Figure 6. *Dr. Beard in 1950.*

the tragic death of his brother, for which he was blamed, caused Dr. Beard to keep his distance from acquaintances for fear of being hurt. This behavior was not unknown to Joe. He said, "Familiarity is never desirable with superiors because it is dangerous; with inferiors, because it is unbecoming; least of all with the common herd, who become insolent from sheer folly; they mistake favor shown them for the repeated need felt for them. Familiarity trenches on vulgarity."

As a student of "Dog Surgery" with Dorothy and Joe Beard I became their target. A sterile technique along with a fifteen minute scrub with soap and water was repeated three times (45 min) for my first class. A square knot, two hand tie, was also a requirement. Their practice of riding my back gained me the sympathy of my classmates. My classmates surely felt I would not make the grade. Our confrontations were punctuated by Dr. Beard's comment, "You are going to be the damnedest surgeon I've ever trained whether you like it or not." Those words ended our arguments over their demeanor toward me in the "Dog Surgery" class.

Occasionally I would go to spend the weekend at Dr. Beard's farm. I could mimic his vocabulary with the "hell and damn" to perfection. The weekends spent with Joe during medical school helped me to understand his demeanor and personality. I spent much time listening to his philosophy of life. He was the best read man and he could talk on any subject. He read not only paper pulp westerns, but also poetry, and every novel and scientific periodical he could get his hands on. He was truly the wisest man I ever knew. He spoke and wrote in five languages, four of which were self-taught. He was intolerant of intellectuals who were only fools. He respected the superior intellectuals of truth. He believed in God, but had little tolerance for most preachers since their knowledge was sparce and they were unable to communicate intelligently with him on Biblical matters. He said, "McIntyre, man has one purpose on earth — either to reproduce himself or to grow something that would be lasting when his Maker calls. My papers are my children and a lasting contribution to mankind. When man can no longer make a contribution he has no reason to be here." This remark provided me with great insight into the last days of his life.

"Never have a companion who casts you in the shade." This best described Dr. Beard's philosophy; this is not to imply he was not friendly to any acquaintance. He worked with farmers around him and looked like a day laborer on the weekends. He cut hay, fertilized fields and milked dairy cows on the farm. His fields were immaculate; as the cows were milked he collected urine and feces in a trough that ran into a vat. In the spring he would fertilize his fields with this through a spray attached to a tractor. He truly was a leader in the Biblical sense for he was a servant to all.

While I was a student at Duke he set up the first electron microscope; I was present in the laboratory when the analysis of the chemical make-up of the virus was found to be a single strand of DNA.

In 1963, Dr. Beard broke his tibia and fibula in both legs in an automobile accident. Most men would have given up because healing was slow, but not Joe Beard — tenacious beyond imagination. After one and a half years of healing



Figure 7. *Dr. Beard in 1970 on the Duke University Medical School campus.*

which left him two inches shorter, he was able to work, but not without pain.

Joe received many awards but never mentioned any after his first disappointment. He received the Clowes Cancer Memorial Award for his work on leukemia in chickens. He established the relationship of a virus causing and resulting in the transfer of leukemia in chickens. Shortly afterward he was asked to be the Southern lecturer for the Sigma XI Society (figure 7). For one year he lectured at every university and college in the South. The first lecture was poorly received because he used perfect grammar. Recognizing that this was not his way of lecturing, he inserted his customary "hell and damn" and became an immediate success. He lectured to full houses thereafter and students from one school, after hearing him, would follow to the next speaking destination. Believe me, he could use those two words for emphasis and no one would ever think anything of it. His virus lectures and dog surgery classes were never dull with his "artful" usage of these words. Shortly before his retirement from Duke, at the age of 70, he received the Borden Award by the American Associa-

tion of Medical Colleges. He was made a James B. Duke Professor on the faculty of Duke. In 1977, he received the Distinguished Teacher Award by the Duke Alumni Association.

After leaving Duke he became head of the Commercial Life Science Laboratory in St. Petersburg, Florida. He was a pioneer in molecular biology. He shipped virus all over the world that produced an enzyme, reverse transcriptase, which acted on bacteria. This virus in simple terms recombined DNA or caused gene splicing. His work in this field resulted in laboratories being established all over the world of a biogenetic nature. While at this laboratory these scientists created the first mumps vaccine, which is presently in use.

After leaving Duke, Dr. and Mrs. Beard and my wife and I exchanged visits several times. Once in 1974 he developed coronary insufficiency and was hospitalized in the ICU for twenty-four hours in Minden Medical Center, Minden, Louisiana.

In December 1982, Dr. Beard called me from St. Petersburg, Florida. He stated that he had been fired, and he wanted me to hear it from him first. He was 81 years old and I told him it was the best thing that ever happened to him. Upon investigation, I discovered he had not been fired, but when told to increase the price of the virus shipped by 100%, he quit. At my insistence he came to my home three weeks later. I noticed on the first night at dinner, every time he swallowed he coughed. I questioned him and learned this recurring problem had been getting progressively worse. He had lost fifteen pounds. The following morning a barium swallow revealed a Zenker's diverticular. At my suggestion that he return to Duke or some other prestigious place, he retorted "Why should I go anyplace else, when I know and have seen your work?"

The repair of the diverticulum was smooth and with hyperalimentation via tube feeding he soon gained twelve pounds and looked good. After two weeks of tube feeding he continued to cough when receiving food. Observation revealed a refusal to move the trachea upon swallowing. Three weeks after surgery he developed an incarcerated hernia. He refused to reveal this to me so the following morning Dorothy told me. Under local anesthesia I reduced and repaired the hernia. After two more weeks I threatened him with the nursing home if he didn't raise the trachea up and swallow properly. He started swallowing properly and I took him to my home, and with nurses around the clock for six weeks, he gradually but progressively improved.

Dr. Beard returned to St. Petersburg, but two weeks later was again hospitalized with a refusal to swallow properly. He had become a deliberate anorexia nervosa. Two months later he had lost twenty pounds more and his chest x-ray revealed oatcell carcinoma of the lungs. He died in less than three weeks.

Shortly after Dr. Beard's death, Dorothy Beard, who had both breasts removed for carcinoma about fifteen years before, developed carcinoma of the uterus. She died three months after the onset.

In October of 1984 my wife and I returned to the home of Dorothy and Joe Beard. The house was bare, and weeds had grown up everywhere. Over the garage was an office that was open. There was a bookshelf with two empty shelves, but on the bottom shelf was a book of poetry with the front cover missing. The book had been used at Centenary College by Dr. Beard. It had been a gift from George P. Evans, a professor visiting from Oxford, England. Inside the book were checked poems composed by Hewick, Lovelace, Suckling, Shakespeare, Milton and others. All poems checked dealt with love or sorrow. We then visited the old Episcopal Church cemetery in Hillsboro, N.C. where Dorothy and Joe were buried. Two small metal sticks with 3 x 5 inch cards marked their graves. Thus ended the era of a great man and his wife.

Dr. Beard was a scientist, surgeon, teacher, philosopher, dairy farmer, world traveler. What he accomplished in 81 years was more than could have been expected of ten men. He lived a controlled life, well planned, with no vision impossible.

Dr. Joe Beard was a genius who lived with tragedy. The expression of outward emotion, compassion, love, or gentle words were avoided. Tenacity beyond reason, kindness without show, courage in all convictions, unshakeable in character and humble to man, all describe Joe Beard as I knew him. "Adversity is strength" he told me one cold, snowy day. One must wonder what Joe Beard would have been with a loving mother, without the tragic loss of his brother, and with a successful first marriage with children.

Within myself I find these lines quite appropriate, "I loved you, not for what you were, but for what I was when I was with you. I loved you not only for what you made of yourself, but more for what you made of me."

A poet I am not, but I feel the following lines sum up Joe Beard in my lifetime:

I met a Man a day or two ago
Oh, I had heard of him, mostly
Bad and So and So
But when I met him
What I heard began to fade
Because you see, of me
A personal friend he had made.

We walked a bit and talked
a bit, and finally just us two
settled down to think as
the spring sky turned blue.
And in his conversation then
to me, his heart laid bare;
And friendship was the thing
for which we had a flare.

I think we are going to be OK
that man and me
Because the hardest part is
over and we trusted each
other, you see
And this I believe with
all my heart and soul
Our God stands and smiles,
as this story unfolds.

Dr. Joseph Willis Beard was a *mighty fine example* of what the Master had in mind when He said, "I will create a man."

Joseph Beard is one of the people who made the present Duke University Medical Center possible. He was the first member of the clinical departments to establish laboratories outside of the Departments of Anatomy, Physiology, Pharmacology, Bacteriology and Pathology. He was the first clinically trained scholar at Duke to be supported by research monies rather than by practice-generated funds.

When Duke Medical School opened, the decision was made that the clinical departments would have no laboratories. The clinician would collaborate with a member of the preclinical faculty. I was the first person to break this mold and establish a laboratory in a clinical department. When I came to Duke in 1947, I established research laboratories in the space assigned to Medicine. Walter Kempner had laboratory space, but it was in the space assigned to Physiology. All departments at Duke were being strangled because the preclinical faculty refused to expand outside of space physically attached to the medical school-hospital complex. They drew up plans for expansion each year, but they could not find the money to expand in Duke stone. Joseph Beard broke the bottleneck. He moved across the railroad tracks into a simple, two-story, expandable brick building. Dean Davison was so unsympathetic that for years the approach to Joe's building (named the Bell Building) was by a dirt trail that turned to mud with each rain. I joined up and helped finance the second floor of Joe's building. From then on, research endeavors in Medicine and Surgery were free to grow. Every few years we bought bricks and added space. Finally, Philip Handler, the Chairman of Biochemistry, joined up and moved his department into Bell Building. Duke was on its way as a major research center.

Beard ran his building with an iron hand. Every room had to have steam. There was no other way to insure sterility. No equipment was allowed in the corridors. If you didn't use your space, it was quickly assigned to others.

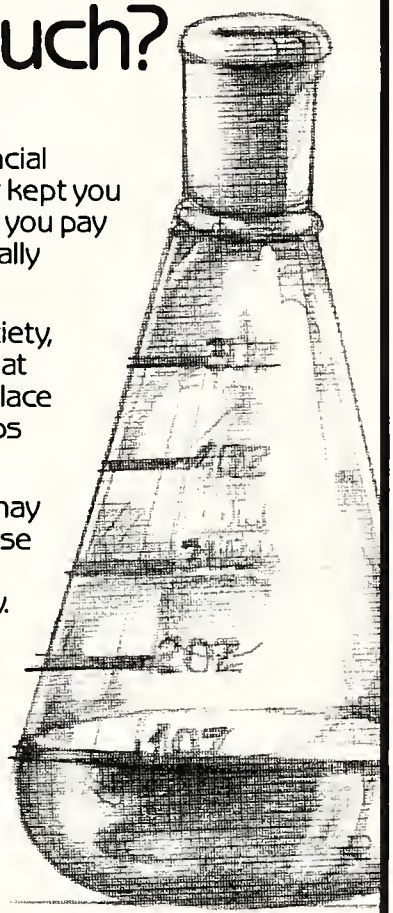
I bought a concrete mixer from Sears. I had no trouble in mixing cement, but I allowed mortar to crud the mixer. I went to see Joe at his farm. He showed me how to chip out the mortar and instructed me how to keep the mixer clean. During this time, he was raising chickens for his chicken leukemia studies. He supplied us with free chickens. I always hoped they were from the controls.

The Dorothy and Joseph Beard Research Fund, created by patents on equine encephalitis vaccine, supported the laboratory until the National Cancer Institute took over. The residual estate of Joe and Dorothy Beard will eventually contribute over a million dollars to support research at Duke.

One of the great men of Duke — Joseph Beard.

Eugene A. Stead, Jr., M.D.

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Book Review

Diane C. Cashman

Wilmington Yesteryear *by Robert Martin Fales, M.D., 152 pages plus index, 255 black and white photographs, published by the Lower Cape Fear Historical Society, P.O. Box 813, Wilmington, NC 28402. $28 (including N.C. sales tax, handling, and postage).*

On February 15, 1985, Wilmington's oldest practicing physician, Robert Martin Fales, M.D., retired from practice. His half century of medical service spanned an era marked by momentous change. Fortunately, Dr. Fales's memories of those changes have been captured in his informal memoir and pictorial history, *Wilmington Yesteryear,* which was published under the aegis of the Lower Cape Fear Historical Society in December 1984. As "Heartbeat," the in-house publication of the New Hanover Memorial Hospital, noted, Dr. Fales's book provided "an immortality" to the physicians of yesteryear.

Dr. Fales can still remember his return to his hometown of Wilmington in 1935 and his entry into the private sector of the medical profession: "My first order of business upon return was to find office space. Some of the well-established physicians maintained offices in the Murchison National Bank Building, but I was in no position to aspire to such lofty heights. Many doctors still practiced from offices located in their homes, and so I felt grateful to my mother, who had been widowed ten years, when she offered a downstairs room of her house as an office . . . (which) was ideal, since it had a separate entrance. I hoped it would not be too long before patients made their way to its door. I unpacked my books and diplomas, made courtesy calls on the local physicians, and made it known that I would be available for both day and evening office hours and would be happy to make house calls after dark. . . . At the end of my first month I had collected twenty-two dollars in cash and felt that those earnings represented a good start. In those days a doctor was supposed to start at the bottom and work up, and I certainly started at the bottom."

If Dr. Fales "started off at the bottom," he ended "up at the top" for in his half century of service he became one of Wilmington's most popular and respected physicians. In recent months he has also become one of the area's best selling authors. This new development resulted from the publication of *Wilmington Yesteryear*. Dr. Fales's keen memory, candor, and humor make his book delightful to read, although from his point of view the book's value is in its 255 photographs, which were selected from his historical slide collection that tops 1,100.

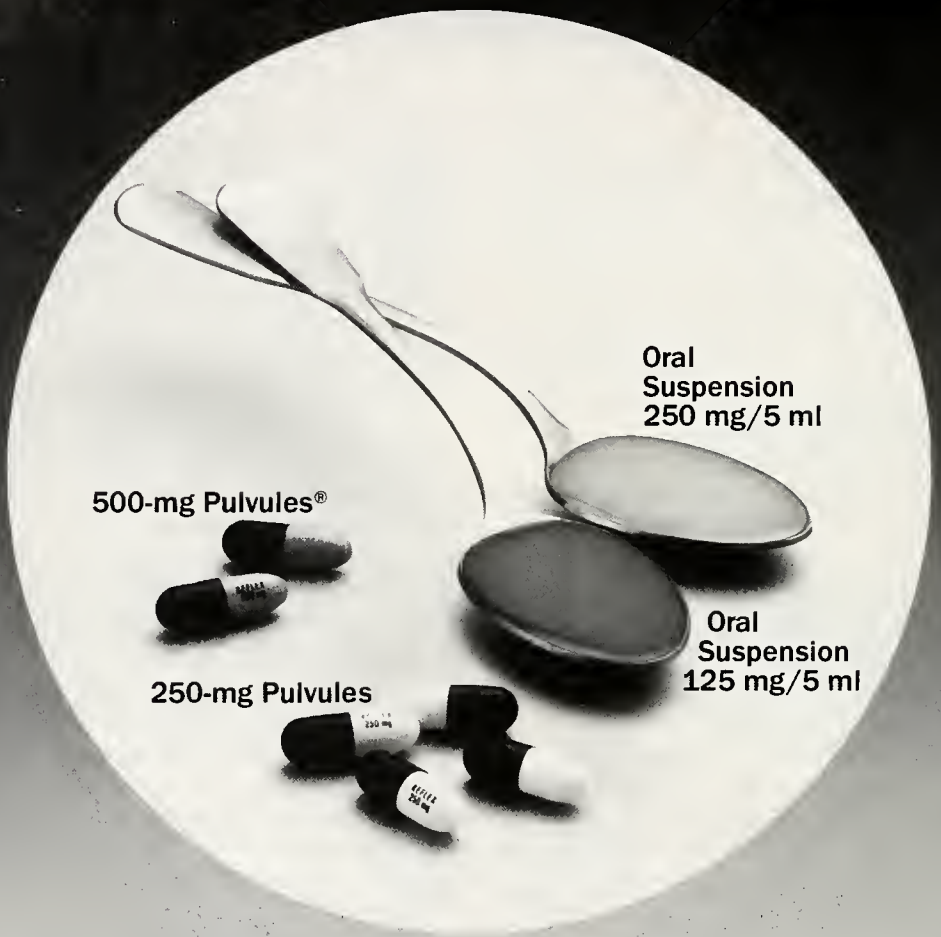
The book takes the reader back to the Wilmington of Dr. Fales's childhood, when the port city was cooled by ice and powered by steam. The characters that impressed him: hearty Masonboro Sound fishermen, dashing firemen, proud Confederate veterans, strict maiden lady school teachers, and German shopkeepers all come to life in picture and word.

Dr. Fales devotes one chapter to his medical education at Wake Forest and Jefferson Medical College, to his practice in Wilmington, and pays tribute to the physicians and nurses of the "old school." A faded photograph shows surgeons operating without masks or gloves and the author recalls a surgeon stating that there was no need to scrub "because a gentleman's hands are always clean!" The medical chapter also includes photographs of Wilmington hospitals that have gone out of business: James Walker Memorial Hospital, Babies Hospital, and Community Hospital and includes a section on the James Walker Memorial Hospital School of Nursing.

Wilmington Yesteryear has received warm reviews and media coverage, and enjoyed brisk sales. The book's success is no surprise to those who know Dr. Fales. For more than a half century he has touched his patients' lives in a meaningful way and earned the respect of his professional colleagues. When Dr. Fales was autographing books at a local store, a customer was heard to say, "I bought this book so I can hold in my hands what Dr. Fales has meant to me."

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IN STATE

May 17-18

Neurosurgery Laser Workshop
Place: Chapel Hill
Fee: $700
Credit: 15 hours Category I AMA; AANS-CNS
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 22

Antibiotics — The New Ones
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

May 23

Sexually Transmitted Diseases
Place: Chapel Hill
Fee: $20
Credit: 5 hours Category 1 AMA
Info: CME Office, 231 MacNider 202H, Chapel Hill 27514. 919/962-2118

May 24-25

Diagnosis and Treatment of Pediatric Hypersensitivity Diseases of the Lung and Gut
Place: Durham
Fee: $80
Info: Alexander Spock, M.D., Box 2994 DUMC, Durham 27710.

June 4

Crisis — Then & Now
Place: Charlotte
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

June 10-12

Surgery for Coronary Artery Disease
Place: Durham
Info: Robert H. Jones, M.D., Box 2986 DUMC, Durham 27710.

June 13

32nd Annual Mountaintop Medical Assembly
Place: Waynesville
Info: Debbie Ford 704/452-4772

June 13-15

Advanced Clinical Ultrasound
Place: Winston-Salem
Fee: $400
Credit: 16 hours Category I AMA
Info: James F. Martin, M.D., Box 229, Bowman Gray, Winston-Salem 27103. 919/748-4505

June 19

Cutaneous Manifestations of Systemic Illness
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

June 20

Crisis — Then & Now
Place: Elizabeth City
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

June 23-28

NC Health Promotion Wellness Institute
Place: Raleigh
Credit: 27 hours Category I AMA, AAFP
Fee: $260-370
Info: Jacqueline Rollins, Wake AHEC, 3000 New Bern Avenue, Raleigh 27610. 919/755-8018

July 5-7

15th Annual Sports Medicine Symposium
Place: Wrightsville Beach
Info: Alan Skipper, NCMS, Box 27167, Raleigh 27611. 919/833-3836

July 11

Crisis — Then & Now
Place: Hickory
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 15-19

Sonography of the Abdomen
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

July 16

Crisis — Then & Now
Place: Wilson
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

OUT OF STATE

May 25-27

Gynecologic Urology and Pelvic Surgery
Place: Hot Springs, VA
Fee: $250
Info: Eileen Hardigan, Box 538 MCV Station, Richmond, VA 23298. 804/786-0693

June 6-8

Rehabilitation of the Brain-Injured Adult and Child
Place: Williamsburg, VA
Fee: $275
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

June 12-15

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Fee: $350
Credit: 15.5 hours Category 1 AMA, AAFP, NCMS
Info: Division of Dermatology, Box 3135 DUMC, Durham 27710. 919/684-2504

June 27-29

Bones, Joints, and Sports Injuries
Place: Virginia Beach, VA
Fee: $275
Info: Beth Winn, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

July 1-6

Mid-Summer Family Practice Digest
Place: Myrtle Beach, SC
Fee: $300
Credit: 30 hours AAFP
Info: NCAFP, Box 20146, Raleigh 27619.

July 19-21
5th Annual MCV Cardiology Conference
Place: Hot Springs, VA
Fee: $275
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

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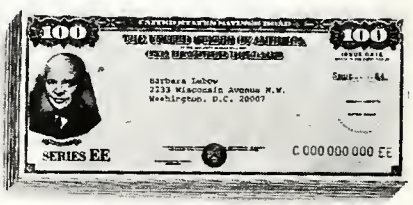


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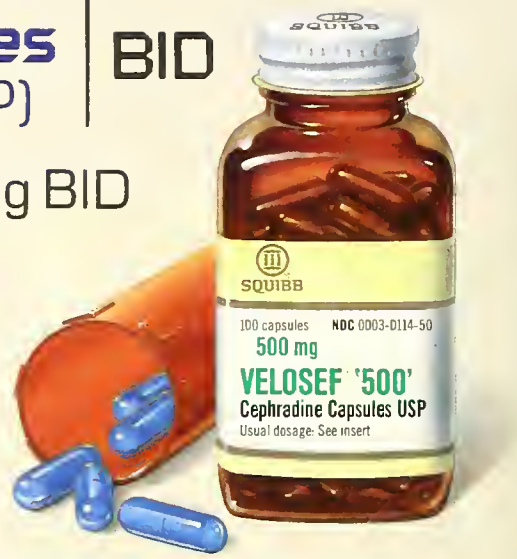
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INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli, P. mirabilis, Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

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Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers: Since cephradine is excreted in breast milk during lactation, exercise caution when administering cephradine to a nursing woman.

Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Hematologic — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

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Letters to the Editor

Blood and the Jehovah's Witness

To the Editor:

I continue to enjoy the *North Carolina Medical Journal*. I have just read the February issue from cover to cover. I was most intrigued with the Physician's Forum concerning patients who refuse life-saving treatment.

I had a recent interesting experience with a Jehovah's Witness. She originally refused to have blood before surgery to remove a large cystic thecoma. We were willing to operate without transfusions out of our respect for her religious belief. Prior to surgery she changed her mind and received two units of red blood cells. The operation was successful but unfortunately she developed postoperative bleeding from post-transfusion thrombocytopenic purpura. She is probably the first and only Jehovah's Witness to develop this condition because they are rarely transfused. She was treated by plasmaphoresis on two occasions and recovered uneventfully.

Post-transfusion thrombocytopenic purpura is an exceedingly rare complication, only 30 cases having been reported in the literature through 1980.

This patient was nearly smarter than her doctors!

Robert K. Yowell, M.D.
2609 North Duke Street
Durham 27704

Physicians in the 1985 Legislature

To the Editor:

Having known Harold R. Silberman, M.D., for over twenty years, I was not surprised to see the excellent editorial he submitted regarding physician involvement and interaction with the members of the 1985 North Carolina Legislature. Harold wisely and appropriately reminds us that physicians should and must "become involved" with pending legislation that affects not only the practice of medicine, but more importantly, the preventive medicine issues.

After observing tragic emergency room cases resulting from nonuse of seat belts by adults, or lack of child passenger restraints, or even those sometimes severe injuries resulting from motor-cross racing, who is better able than physicians to alert our community to the "medical" pros and cons of the bills under consideration.

It goes beyond just volunteering to be a "key-contact" physician. I have volunteered and served as a key-contact physician for several years. I have found this to be a stimulating, rewarding, and very productive experience. I have written to each of my legislators indicating my interest in being available to them to discuss or offer insight on any issue that I might be able to explain from organized medicine's perspective as well as from the perspective of an individual tax-payer. I basically believe that most of the issues that physicians can be helpful in are not partisan at all, and I personally have had no difficulty whatsoever as a registered Republican getting heard by and interacting with responsible Democratic legislators. I was not clever enough to provide my paging beeper number to my state representative and/or senator, but I think Harold provides a useful suggestion in his editorial, which I will follow up on.

The point is, we need to stay in touch with our legislators and be "available" in an ongoing sense other than simply waiting until some threatening issue comes up to begin a frantic "lobbying" effort. I commend Harold for his editorial and for his efforts to take the time to get involved.

F. Maxton Mauney, Jr., M.D.
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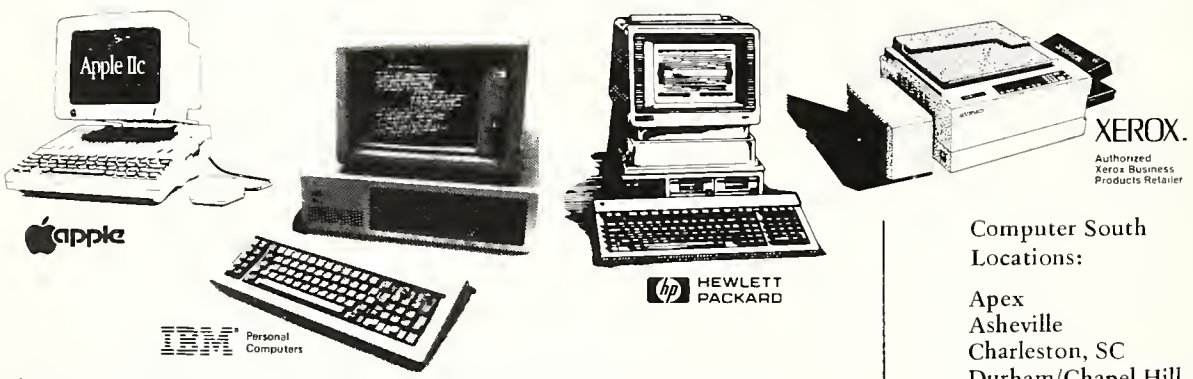
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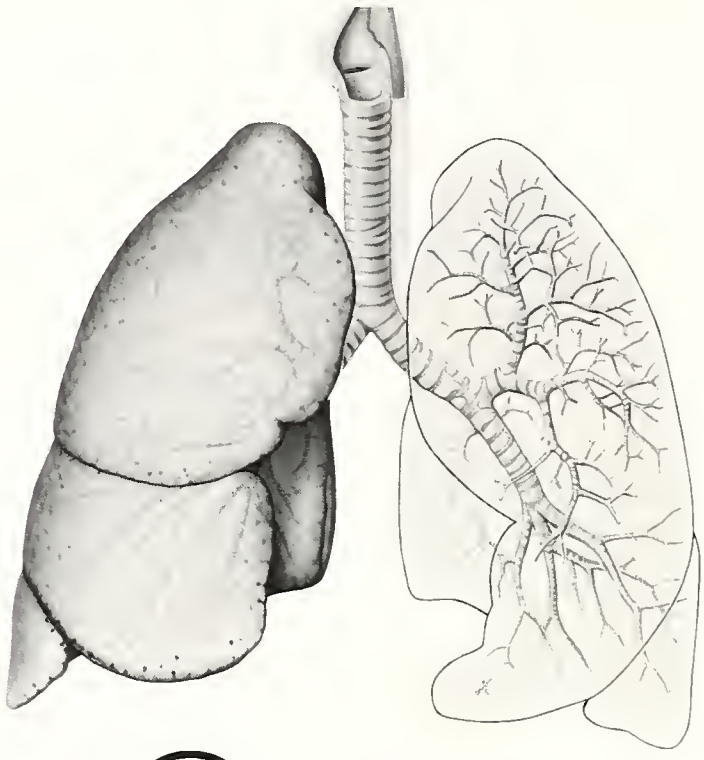
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Indications and Usage. Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

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Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication. Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions. Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0617B2R]

Note. Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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SPECIAL ARTICLE

Family Medicine at Duke: Excellence Defined

Robert J. Sullivan, M.D.

THIS month at Duke, the Life Flight helicopter was inaugurated, the state's first human heart transplant was successfully completed, and the Family Medicine program was scheduled for termination. Duke is clearly on the move, and the direction seems increasingly clear. Each of these events has been accompanied by some controversy, particularly the Family Medicine decision since it simultaneously affects so many people throughout the region and perhaps elsewhere.

The Family Medicine residency program was inaugurated at Duke in 1972 owing to a fortuitous set of circumstances. Federal and state money was available, the department of Community Health Sciences headed by a respected faculty member wanted the program, and community physicians were pressing Duke to re-establish a commitment to primary care in the state. Until 1947, Duke was heavily oriented toward clinical practice under the leadership of Dean Davison. The expansion of federally funded research programs following World War II was greeted with enthusiasm by the faculty who successfully garnered major support from this resource. The school grew rapidly and the specialists, sub-specialists, research-oriented physicians and Ph.D.'s soon outnumbered those generalists who treated patients not requiring the services of specialists. Although uneasy about this transition, Dean Davison could not prevent it. Following his retirement, his medical center successors further expanded the growing image of Duke as an innovator in medical research and as a referral source for the southeastern region.

Of course, Duke was not alone in this technologic thrust. Most major medical centers were following much the same course. By the mid-1960s the family medicine movement arose nationally to re-define the role of physician generalist. The generalist concept was not universally hailed with enthusiasm by medical center specialists. Particularly those in pediatrics, internal medicine and obstetrics/gynecology were skeptical that one person could know enough to do the job well. Perhaps more disturbing was the perceived criticism of the way specialists were conducting business. In effect, the family practitioner seemed to be laying claim to the mantle of "physician" while others were relegated to the role of "doctor."

To the degree individual teaching institutions felt motivated to respond to the call, family medicine programs sprang up throughout the nation. However, for a multitude of reasons, few privately-endowed medical centers in Duke's circle of equals took the plunge. When Duke, after rejecting two proposals, finally proceeded in 1972 to create the Family Medicine program, it was not done with unanimous faculty acclaim.

Logic dictated the new program be placed in the local community hospital where an enthusiastic group of practicing primary care clinicians and specialists welcomed the strengthening of their own residency program. Duke University Hospital, already overcrowded with referral patients, staffed by subspecialists and replete with a full complement of house staff, remained off-limits to the new program faculty and house officers. This arrangement meant the new Family Medicine program was out of sight, but not out of mind.

Under capable leadership, the Family Medicine program at Duke rose to national prominence. It served the region by producing a substantial number of primary care physicians who located throughout the state. The program emphasis on community care provided a point of identity and contact with Duke University for many who long felt estranged from the technologically oriented medical center. Duke became eligible for Area Health Education funds as a result of its production of primary-care physicians and through participation in the statewide network of education. The family medicine movement got a tremendous boost from the presence of training programs at all four medical schools in the state, the largest of which was located at Duke. The medical center reputation as a good citizen was enhanced throughout the state. Unfortunately, internal problems persisted.

The resident and faculty physicians at the Family Medicine center were located on the campus of Durham County Hospital three miles from Duke Medical Center. Their daily working relationships with community specialists led them to refer many patients to the physicians at Durham County Hospital. Absence from Duke Medical Center inhibited their knowing which Duke specialist to call upon when addressing a particular patient's problem. Primary care physicians are acutely aware of their responsibility for coordinating care and feel uneasy referring patients when they don't personally know the specialist. In addition, patients sent to the Medical Center complained about problems with parking, delays in the clinic and high costs when compared with community options. In prior years, the absence of alternatives would have made the trip to Duke inevitable. However, the growth of medical expertise in the Durham community, largely a result of Duke's own spe-

From the Department of Medicine, Duke University Medical Center, Durham 27710.

cialty training programs, increasingly offered excellent alternatives which many patients specifically requested. Duke perceived its successful thrust in the area of family practice to be diverting patients to community physicians rather than expanding the Duke referral base.

A surprising paradox developed simultaneously as community physicians came to perceive the Duke Family Medicine program as an intrustion into community practice that diverted patients from their offices. When pre-paid practice plans arrived, they were initially viewed by community physicians with disdain until the Family Medicine program jumped at the opportunity and promptly expanded its service population. A ground-swell of uneasiness was building within the community. Local physicians loved the resident services at their hospital, but had not realized when they sought affiliation with the Duke Department of Community and Family Medicine that this new brand of resident and support faculty would establish their own office complex and compete for available patients. Many saw use of the Duke name (Duke Family Medicine Center) as an unfair advantage and pressured the University to limit the function of this new creation.

Additional criticism of the Family Medicine program came from the Duke Medical Center Internal Medicine, Pediatrics and Obstetrics/Gynecology house officers and their attending physicians from Duke who accepted responsibility in rotation for supervising the training program on the wards at the Durham County Hospital. They had trouble understanding the orientation of the Family Medicine house officers who had been carefully selected for their intellect, orientation to patients and their families, and commitment to community needs. The medical center personnel interpreted lack of interest in bench research and pursuit of balanced working hours as evidence of inferior commitment and ability. In reality it was a clash of cultures.

Thus, the Duke Medical Center administration was beset with complaints about the Family Medicine program from three sides. This internal tension was largely unappreciated outside the walls of the Medical Center or the Durham community.

Faced with escalating costs and dwindling resources, the leadership of Duke Medical Center initiated a self-assessment in 1984 to determine areas of unusual strength or expertise on which to place emphasis in the next decade. Family Medicine was given a low priority in this review. When the current Family Medicine division chief (Samuel Warburton) announced his resignation in early 1985, it became imperative to decide the fate of the program. If it were to continue, an intensive recruitment campaign was needed for a successor. And with that campaign came the need for a Medical Center consensus and re-commitment to family medicine. That consensus had become increasingly unlikely.

Since objective internal assessment of the Family Medicine program was impossible, an outside consultant was sought to assess Duke's primary care options in the next decade. The report by Lewin and Associates of Washington, D.C. provided some additional insights and options.

The study called for an independent and dedicated effort in primary care. Noting the specialty orientation of the Departments of Medicine, Pediatrics and Obstetrics/Gynecology, the Lewin report suggested Family Medicine be given expanded responsibility in this area. The success of the program in reaching out to the community and its value as a point of contact for rural physicians and hospitals was emphasized. It was also seen as a valuable resource for future medical center participation in the pre-paid practice movement.

The report also carefully noted the long-standing friction between the Family Medicine program and the rest of the Medical Center. It traced the problem to differing sets of values, equally strongly held. Both groups were committed to excellence; but their definitions diverged. Family Medicine (holistic, integrative and humanistic) challenged deep rooted traditions in academic medicine and clinical practice. The report noted that the decision about the future of the department must resolve these fundamental problems.

The Medical Center faced a clear choice. The Family Medicine program could not continue without a leader. Recruiting a replacement meant either maintaining the program's isolation or full acceptance in the Medical Center. The latter concept was neither practical nor acceptable to the department chairmen at Duke. With the current state of tension likely to persist indefinitely, recruiting a capable leader for Family Medicine would be impossible. Accordingly, with reluctance, the decision was made to close all clinical programs of the Department of Community and Family Medicine and relocate them to newly-expanded primary care divisions within the Departments of Medicine, Pediatrics and Obstetrics/Gynecology. Primary care would henceforth develop at Duke within specialty lines. The conflict was resolved.

Or was it? The magnitude of the decision and far-reaching ramifications have only now begun to surface. More will surely emerge in the ensuing months and years. The Department chairman (Harvey Estes) resigned his chairmanship, and began a movement for keeping a Family Medicine Program — not allied with Duke — alive. Family Medicine forces throughout the state and nation took personal afront and openly criticized the decision. Duke's contractual arrangements with the Durham County General Hospital were thrown into doubt. Capitation funds from the state for training physicians were brought into jeopardy. The Student Health and Employee Health programs for the University were suddenly threatened with relocation and loss of existing staff. The Departments of Medicine, Pediatrics and Obstetrics/Gynecology suddenly were faced with responsibility for ongoing care of a large number of Family Medicine patients who might wish continual service from Duke. The uncertainty surrounding this transition was reflected in newspaper interviews published daily.

Beyond the details of the Family Medicine program closure lie some very large issues that will be of major importance to Duke in the years to come. Our system of medical care financing is undergoing a revolution. The impact is sure to be as great on all medical centers as was the arrival of federal research funding following World War II. The public is unhappy with existing health care arrangements and feels they are too costly, too technical, lacking in personal attention, and inconvenient. Pre-paid practice plans will compete for consumer participation by

satisfying their demands. A doctor surplus will make it possible to hire the manpower to provide whatever services people want in a fashion they desire. Integrated organizations combining insurance, management, financing and professional services from primary care through secondary and tertiary levels will dominate the medical care picture. Medical centers will dwindle in stature as this movement gains momentum. Viewed in this light, Duke's decision to truncate its excellent primary care operation and community access link represented by the Family Medicine program seems to many persons to be most unwise.

Viewed in another light, Duke could be said to have had no choice. Future federal funding for family medicine manpowered training is in jeopardy. Family Medicine had developed no base of research funding. The Family Medicine program, if it is to survive, must garner pre-paid health plan support. But cost-competitive health care is impossible at a training site. When alternative practices open in the Durham area, the Family Medicine program risks being underbid. In addition, effective integration of noncompeting delivery components is essential for any organization that expects to meet tomorrow's market. In 13 years of operation, the program had not created significant bonds with existing clinical departments. The off-campus site and Durham County Hospital connection made true long-range Family Medicine integration with Duke University Medical Center difficult if not impossible. Relocation to the Medical Center was educationally unsound and politically impractical.

The Duke University faculty have previously made difficult decisions. In the past five years, they closed the School of Education and the Undergraduate Nursing program. The Forestry School barely escaped a similar fate but pulled itself from the precipice by diligent effort. Any major corporation faces such tough decisions from time to time. If a valuable subsidiary, no matter how pertinent to long-range future growth, is proving destructive to the fabric of the organization, it must be set free. So it was with the Family Medicine program at Duke.

We come again to the events of the month. Judging from initial utilization, the helicopter service has met a great need. The pioneering efforts of the surgery service in transplant technology have received national attention. Interviews with beleaguered Family Medicine faculty are receding. As with the Schools of Nursing and Education, this too will pass. The Duke University Medical Center faces, as it always has, the awesome continuing task of competing successfully in today's changing climate for recognition as a regional and national resource. Such an effort requires continual growth, trial and reevaluation. It does so now with redefined clarity of purpose and unity of spirit . . . for better or worse. At least it can be said that Duke tried while few of its peers even made the attempt. The Family Medicine program Duke created was recognized as one of the best. It is indeed unfortunate for many, both within the University and throughout the state and region, that the trial proved unsuccessful.

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SCIENTIFIC ARTICLE

You're in for a Treat: Asparagus

Jeremy Sugarman and Francis A. Neelon, M.D.

• *Many people notice an unpleasant odor to their urine after eating asparagus.*

A 47-year-old white married man who had always enjoyed excellent health telephoned the physician's office worried that he might be seriously ill. After working in the garden the previous day, the patient noted a disgusting, "sulfurous" smell to his urine. He was concerned he might have been poisoned in someway, but otherwise felt well. On questioning, the patient recalled eating asparagus at supper the day before. He was reassured that many people notice a characteristic odor in their urine soon after the ingestion of asparagus and his "symptom" would probably be relieved if he avoided asparagus. The patient was instructed to call back if his urine remained fetid without the prior ingestion of asparagus. Of interest, the patient had eaten asparagus several times before and had not noticed the odor in his urine, although he remarked that the smell was "not unfamiliar." A follow-up telephone call to the patient one week later confirmed that the patient had not eaten any more asparagus and the smell of his urine had returned to normal.

Although it was easy to reassure this patient of his "normality," we began to wonder about what actually caused the characteristic odor of urine following the ingestion of asparagus. Is there a specific compound produced as asparagus is metabolized? If so, do all people produce the compound? How come the patient only now noticed a smell in his urine and had not on those previous occasions when he had eaten asparagus? We were fascinated by what we found as we investigated these questions and surprised by the number of people who found the topic interesting. Indeed, it is a subject which has fascinated people from all walks of life, from potentates to peons.

The Role of Asparagus in the History of Medicine

"Before asparagus was used as a food it had quite a reputation as a medicine for almost anything from the prevention of bee stings to heart trouble, dropsy, and toothache!"[1] In the Greek herbals, Dioscorides claimed that asparagus "doth mollifie the belly and prouoke vrine."[2] In the seventeenth century, John Gerarde discussed the virtues of asparagus in *The Herbal or General History of Plants:* "They somewhat provoke urin, are good for the kidnies and bladder, but they yeeld little nourishment to the body, and the same moist, yet not faulty: they are thought to increase seed and stir up lust."[3]

The first mention of the inimitable odor imparted to urine by eating asparagus seems to have been made at the turn of the eighteenth century in a treatise on foods written by Louis Lemery. "Sparagrass eaten to Excess sharpen the Humours and . . . cause a filthy and disagreeable Smell in the Urine, as every Body knows."[4] Before immortalizing Lemery as the esteemed discoverer of the odor, it should be realized Chaumeton gave Avicenna credit for this discovery.[5] Nonetheless, an examination of Avicenna's *Cantos* did not furnish any mention of asparagus whatsoever. In 1732, the noted writer and physician to Queen Anne of Britain, John Arbuthnot, wrote *Practical Rules of Diet in the Various Constitutions and Diseases of Human Bodies.* Under the heading of diuretics, Arbuthnot includes "vegetables which are aromatick and balsamick, Saffron, Asparagus, Nutmeg; those affecting the Urine with a Odour."[6]

Scientific Investigations of the Odor

Over the past century, two approaches have been taken to explain why some people are aware of the characteristic odor of urine after the ingestion of asparagus, while others are not. At first, work focused on identifying a factor in the urine which caused it to smell; those people who reported the odor in their urine became known as "excretors" and those without the odor were in turn called "non-excretors." The first candidate compound was proposed in 1891 by M. Nencki who tentatively nominated a mercaptan (figure 1a), methanethiol (figure 1b), as the etiologic agent.[7] Mercaptans are compounds that substitute sulfur for oxygen in an alcohol group; mercaptans are the odoriferous agents in many pungent substances including skunk spray, garlic and fresh-cut onions. In 1932 Gautier described the rapid appearance of the odor in urine, finding it as soon as seventy-five minutes after ingestion of asparagus.[8] Twenty-five years later, another mercaptan, 2,2′-Dithiolisobutyric acid (figure 1c), was isolated from asparagus. Although the compound has a slight odor, researchers at that time felt it "apparently is not the precursor of the characteristic odor of the urine . . . since no odor resulted when two individuals took 10 mg each of dithiolisobutyric



From the Division of General Internal Medicine, Duke University Medical Center, Durham 27710.

The authors thank Susan C. Smith for the artistic contribution and Marta Conkling for the culinary.

acid orally."[9] A few years later, a methylsulphonium salt of methionine (figure 1d) was isolated from asparagus. Unfortunately, the methylsulphonium salt is an unlikely cause of the odor since it is found in vegetables not causing an odor in the urine.[10] Despite efforts to isolate new compounds, attention returned to methanethiol when Allison and McWhirter[11] gave asparagus to 115 individuals and measured methanethiol in their urine. They found 46 individuals to be excretors, and 69 to be non-excretors, of methanethiol; they concluded "that the excretor character is controlled by a single, autosomal dominant excretor gene."[11] Interestingly, McKusick mentions that a non-excretor may become an excretor during pregnancy.[12]

Because methanethiol is rapidly oxidized, White suspected it could not be the odor-producing compound. He was able to isolate two unusual sulfur compounds in the urine of a subject who had eaten asparagus: S-methyl thioacrylate (figure 1e) and S-methyl 3-(methylthio) thiopropionate (figure 1f).[10] White reported that the addition of these compounds to urine imparted the characteristic odor to previously non-odorous urine. Two years later, other researchers found three, rather than two, novel sulfur-containing compounds in post-asparagus urine, but did not completely characterize them.[13] The difficulty in isolating a specific mercaptan might be explained by the high reactivity of these compounds and their rapid transformation as pH changes. It is obvious that human physiology, for instance in terms of gut bacterial flora or urine pH changes, varies between individuals, and also changes from time to time within the same individual. These variations may well account for the many compounds implicated as causing the odor. We conclude from our review of these studies that the final answer is not yet in! We cannot say with certainty whether (and which) one or many compounds are responsible for the odor of asparagus urine. Nor is it certain that some people do not make the odoriferous compound(s) while others do, but this seems plausible as an extension of Allison's studies on methanethiol.

Figure 1. *Compounds implicated as producing an odor in urine after eating asparagus.*

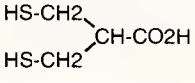
A. A Mercaptan

R-SH

B. Methanethiol

CH3-SH

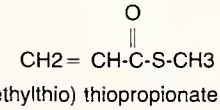
C. 2,2'-Dithiolisobutyric acid



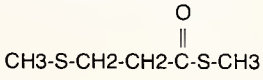
D. Methylsulphonium salt of methionine

(CH-3) 2 S+ CH2-CH2-CH (NH2) COO-

E. S-methyl thioacrylate



F. S-methyl 3-(methylthio) thiopropionate



A fresh approach to the study of the variability in the perception of the odor was taken in 1980, when Blondheim suggested "that the excretion of odorous substances in urine after eating asparagus might be universal, but that the ability to detect their odor varied."[14] Thereupon, the ability to perceive the odor was investigated. In a careful study Lison et al found, "the detection of the odour constitutes a specific smell hypersensitivity. Those who could smell the odour in their own urine could all smell it in the urine of anyone who had eaten asparagus, whether or not that person was able to smell it himself."[14] They found that 10% of 307 subjects tested were "able to smell it at high dilutions, suggesting a genetically determined specific hypersensitivity."[14] The experiments of Lison and his colleagues suggest that at least part of the reports that some individuals do not make malodorous urine after eating asparagus is due to an inability of those individuals to sense the odor at all. Some individuals can only distinguish the smell in a highly concentrated urine — this may explain why our patient "suddenly" became aware of the odor relatively late in life.

An Experiment

Our literature search left us with several questions unanswered regarding the variability in reporting an odor to the urine after eating asparagus. Does everyone make the odor, but only some people smell it? Does everyone smell the odor, but only some people make it? Do both conditions (excretion/non-excretion; perception/non-perception) prevail? To explore these questions, we conducted a small clinical study. Nineteen healthy volunteers (seven men, twelve women) were recruited from the faculty, staff and students at Duke University Medical Center. Urine samples were collected from each subject immediately before the start of the experimental session. Each subject judged whether his own urine specimen had an unusual odor. A small meal of fresh steamed asparagus with lemon and butter, French bread and carbonated water was then served. Postprandial urine specimens were obtained from all subjects. Again each subject was asked to record whether any unusual odor was present. The authors, both known-excretors and known-perceivers, were kept blind of each subject's self report and refrained from eating asparagus during the experimental session. In a double-blind randomized fashion, each author smelled the 38 separate urine specimens and noted whether the urine contained the characteristic odor. The authors resmelled and reached consensus on 10 specimens where there was initial disagreement.

Results. The results of the study are displayed in table 1. Fifteen of the 19 subjects were found to be excretors. One-third of the excretors could *not* perceive anything unusual in their post-prandial urines, while both investigators could. Importantly, 4 of 19 subjects were felt to be non-excretors. That is, the investigators could not detect an unusual odor in their urine.

The authors found it more difficult than expected to accurately detect the odor. Six subjects were found to be false positives; that is, the authors thought their initial urine specimen contained the odor. One of these six subjects had had asparagus for dinner the previous evening, something we had not controlled for. The other subjects were not



Table 1.
Patterns of Excretion and Perception of Odor in Asparagus Urine

Investigator Perception of Odor	Self-perception of Odor		
	YES	*NO*	*N*
Excretors	10	5	15
Non-excretors	1	3	4

questioned about this. Both authors had some difficulty discerning the difference between the acrid smell of a very concentrated non-asparagus urine and a weakly positive post-asparagus urine. One subject was a false negative, reporting he could smell something unusual in his post-prandial urine when neither investigator felt his urine had the characteristic odor.

Discussion. Our results support both theories explaining variability in the odor of urine following the ingestion of asparagus. The investigators, being known perceivers, found that four subjects did not produce an unusual odor after ingestion of asparagus. One of these subjects was able to recognize an unusual odor in a known positive urine. If the theory suggesting that only a variation in sensitivity of smell accounts for the differential recognition of the odor, these data would not be expected since two known perceivers (the authors) could not smell an odor in those four urines. These results suggest that some people are excretors while others simply are not.

On the other hand, five of the fifteen subjects who were excretors could not perceive the odor in their own urine; two of these five subjects were tested against another strongly positive urine and could detect no odor. Thus, it appears that both theories are (partially) correct: some people are excretors while others are non-excretors; some people are perceivers while others are non-perceivers.

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"What cha' plantin', Neighbor?"
"Asparagus."
"Don't cha' know it takes two years to make itself known?"
"Nope! It takes about one hour after you eat it."

AN ODE OR VILLAINELLE FOR ASPARAGUS

Ah, stop time's arrow in its flight!
It takes two long years 'til it appears:
The asparagus stalks by night.

Set the table! For dinner tonight
It's sparrowgrass, a feast served here
That stops time's arrow in its flight.

Supplicants enamored by the sight:
Love's ruddy apple; the green spear
Of asparagus stalks by night.

The taste, the roué palate's delight
Which knows not yet the thing to fear.
Oh, stop time's arrow in its flight.

The Gargantuan fete makes bellies tight;
An urge to miction soon appears —
The asparagus stalks by night.

Behold! The urine's malodorous might,
Enough to make the dry eye tear
And stop time's arrow in its flight;
The asparagus stalks by night!

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SCIENTIFIC ARTICLE

Increase in Health Professionals in North Carolina: 1978-1983

Mary Anne Salmon, Priscilla A. Guild and Shannon P. Hallman

• *Health professionals are increasing in number faster than North Carolina's population, representing real improvement in the supply of health care.*

THOUGH vital statistics and data on health care facilities have long been regularly published in North Carolina, current information on the state's health workers has become available more recently.

Since 1974 the Health Services Research Center, University of North Carolina at Chapel Hill,[1] has maintained data on licensed health manpower in the state through a cooperative effort with each licensure board.

Currently, files are maintained for the following professions:

chiropractors
dental hygienists
dentists
doctors of medicine
doctors of osteopathy
licensed practical nurses
nurse practitioners
optometrists
pharmacists
physical therapists
physical therapy assistants
physician's assistants
podiatrists
psychologists
registered nurses

These files are updated yearly, current as of October 31, based on data from each of ten boards which either license or register these professionals who practice in the state.

Figures 1-3 draw from these files to show the changes in numbers of health professionals which occurred in the five year period ending in 1983. Although North Carolina remains behind the country as a whole in its ratio of doctors to population,[2] these figures, taken together with figure 4, which shows the state's increase in population, indicate that the numbers of physicians and other licensed health workers in North Carolina has increased faster than the general population during that period.

As shown in figure 1, the number of nonfederal, nonresident physicians practicing in the state grew 31 percent (from 6433 in 1978 to 8426 in 1983). However, relatively little of this growth was in the primary care specialties. The number in general practice declined almost 25 percent while the numbers in pediatrics and ob/gyn showed modest increases. The exception to the slow growth trend in primary care was family practice which showed the largest

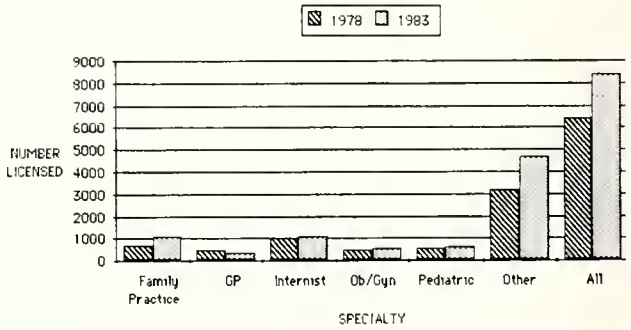


Figure 1. *North Carolina Physicians 1978 and 1983.*

proportionate gain of the primary care specialties. This brought the number of family practitioners in 1983 almost up to the level of internists, the most prevalent of the primary care physicians. By contrast to most primary care categories, physicians in specialties not providing primary care, already the largest group, experienced a forty-six percent increase: from 3204 in 1978 to 4666 in 1983. In 1983, fifty-five percent of North Carolina's doctors were in specialties outside of primary care.

The supply of nurses in North Carolina also grew during the period from 1978 to 1983. Figure 2 illustrates a larger

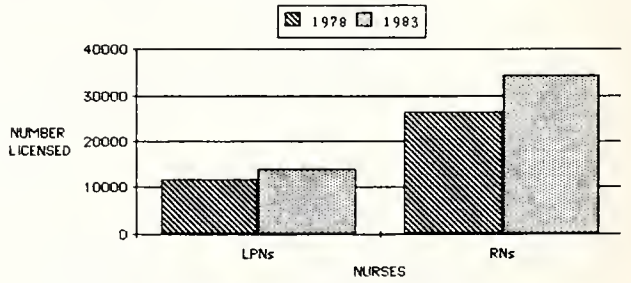


Figure 2. *North Carolina Nurses 1978 and 1983.*

From the Health Services Research Center, University of North Carolina, Chapel Hill 27514.

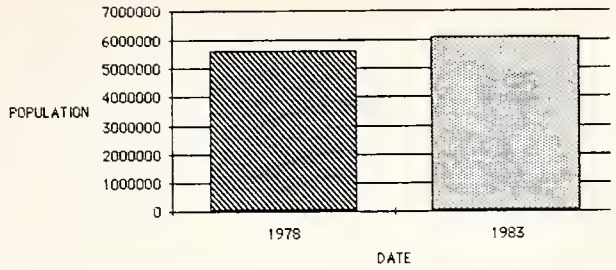


Figure 3. *Other North Carolina Health Professionals 1978 and 1983.*

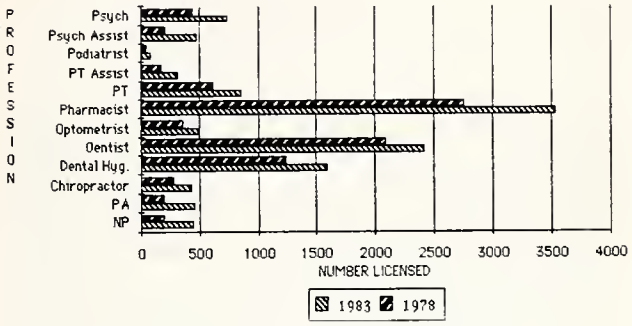


Figure 4. *North Carolina Population.*

increase in the number of registered nurses than licensed practical nurses, both numerically and proportionately.

Growth in the remaining health professions is shown in figure 3. By far the greatest proportional growth was in the ancillary professions. Nurse practitioners, physicians' assistants, and psychological associates[3] experienced growth in excess of 100 percent. Physical therapist assistants also experienced a proportionately large increase in their numbers (78.9 percent). While the increase in the number of dental hygienists was more modest (27.0 percent), it was proportionately greater than the increase in the number of dentists during the same period. Pharmacists were the largest group of licensed health professionals aside from nurses and doctors. Their numerical increase was large (778), but their proportional increase was a modest twenty-eight percent.

Finally, as shown in figure 4, the state's population increased by only nine percent from 1978 to 1983 so that the gain in numbers of health professionals represent real improvement in the supply of health care.

Notes

1. Health Services Research Center, University of North Carolina at Chapel Hill, Chase Hall 132-A, Chapel Hill, NC 27514, Telephone: 919-966-5011
2. American Medical Association: *Physician Characteristics and Distribution, 1982 Edition,* Chicago: Survey and Data Resources, American Medical Association. 1983.
3. Psychological associates are psychologists with a masters degree working under the supervision of a Ph.D. level practicing psychologist.

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SCIENTIFIC ARTICLE

In Vitro Fertilization at the North Carolina Memorial Hospital in Chapel Hill

Luther M. Talbert, M.D., Mary G. Hammond, M.D., Jouko Halme, M.D., Ph.D., Michael O'Rand, Ph.D., Carol Sloan, M.S. and Linda Bailey, R.N.

• *After two years the "test tube baby" program in Chapel Hill has an increasing success rate.*

IN vitro fertilization and embryo transfer (IVF) consists of the aspiration of oocytes from the ovary by way of laparoscopy, fertilization with the husband's sperm, and transfer of embryos into the uterus after a suitable time interval. This paper is a report of the early experience with IVF at The North Carolina Memorial Hospital in Chapel Hill.

The first patient cared for in this program had laparoscopy carried out during February 1983. In that year, 41 patients initiated therapy with human menopausal gonadotropins and 38 underwent oocyte aspiration by laparoscopy. During 1984, 67 patients initiated treatment and 59 had oocyte aspiration carried out.

The protocols utilized at Chapel Hill are similar to those of the Jones Clinic at Norfolk, VA.[1, 2] Patients are accepted if they have irreparable tubal disease, endometriosis not responding to traditional treatment, unexplained infertility, oligospermia, antisperm antibodies, and multifactorial infertility.

All are seen for an initial evaluation by one of the authors (LMT). Screening laparoscopy is recommended in about 30% of patients to ascertain that a significant portion of at least one ovarian surface is visible for oocyte aspiration. At the time of screening laparoscopy vigorous efforts are made using scissor dissection to free up ovaries that are bound by adhesions. It is surprising how often ovaries that are completely covered with adhesions can be made visible by aggressive laparoscopic dissection. If sufficient ovarian surface cannot be brought into view by laparoscopy, patients are offered open laparotomy for this purpose so that the ovaries can be made available for later IVF.

Hyperstimulation aimed at the development of multiple follicles for aspiration is begun on day 3 of the menses. Our usual stimulation protocol consists of the administration of 2 ampules of human menopausal gonadotropins (hMG) daily until the serum estrogen level reaches 400 pg/ml and at least two follicles greater than 14 mm are visible by ultrasonography. Fifty hours after the last dose of hMG, 10,000 IU of human chorionic gonadotropin (hCG) is given, and laparoscopy is carried out 36 hours later. All visible follicles are aspirated and subjected to multiple washes. Follicular fluid and washes are transported to the adjacent laboratory and searched for oocytes using a dissecting microscope. Fertilization is carried out in Ham's F-10 solution with 7.5% fetal cord serum or preovulatory maternal serum. Fetal cord serum is always used when the female partner has been shown to have antisperm antibodies. After 16-18 hours in the insemination medium, the oocytes are transferred into growth medium consisting of Ham's F-10 solution with 15% serum added. Forty-four to seventy-two hours after insemination, all cleaved embryos are transferred into the uterus. The luteal phase is supported with 25 mg progesterone in oil intramuscularly daily and pregnancy testing is carried out 14 days after transfer. If the pregnancy test is positive, hydroxyprogesterone caproate (Delalutin) 250 mg weekly is administered until 20 weeks from transfer.

From the Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology and Department of Anatomy, University of North Carolina School of Medicine, Chapel Hill 27514.

Results

During 1983, 41 patients were started on hMG stimulation. Three cycles were discontinued because of inadequate response, leaving 38 cycles which resulted in laparoscopy. Embryos were obtained in 27 patients (71%), but only one patient established a clinical pregnancy. This pregnancy resulted in a normal liveborn infant.

Because of the unsatisfactory pregnancy rate, the program was closed during November and December 1983. Clinical and laboratory protocols were carefully reviewed by the local staff and by outside consultants. Modifications were made to reduce the dose of hMG, and quality controls in the oocyte laboratory, already stringent, were made more rigid. The program was reopened in January 1984. Pregnancy rates were greatly improved during 1984. Three pregnancies conceived during 1984 have been delivered (1 with triplets) and others are ongoing. The pregnancy data for 1984 are given in table 1.

The pregnancy rate during 1984 was 14% per laparoscopy and 20% per transfer. Two spontaneous abortions occurred. Thus, a woman coming to laparoscopy during 1984 had an 11% probability to obtain a live birth. These data are consistent with results from the major national and international IVF clinics.

Table 1
1984 IVF Data: The North Carolina Memorial Hospital

Started stimulation	67
Discontinued cycle	8
Laparoscopies	59
Transferred embryos	41
Pregnant	8

Discussion

The first human birth as a result of IVF occurred in 1978.[3] By 1982, the pregnancy rate per laparoscopy had risen to 12-15%, and the pregnancy rate per embryo transfer to 18-25%. Taking into account the spontaneous abortion rate, most successful clinics in the world now report that 10-15% of patients undergoing laparoscopy actually achieve a live birth.[1, 2, 4] The procedure, therefore, has become a viable option for treatment of infertility that has not responded to the usual methods of therapy. Although IVF was initially considered to be appropriate treatment only for patients with tubal disease, experience has shown that patients with endometriosis, unexplained infertility, and multiple factor infertility also respond well to this therapy. Indeed, IVF appears to be an effective therapy for male factor infertility, provided 250,000-500,000 sperm survive the washing procedures preparatory to IVF and provided the rate of motility is satisfactory. Pregnancy rates are somewhat reduced in this group.[5]

Appropriate referral of patients to a center for IVF requires an understanding of the concept of fecundability (likelihood of conception) after various treatment protocols have been carried out.[6, 7] Patients who undergo surgery for tubal disease or endometriosis and who do not conceive within 18-24 months are unlikely to do so and should be considered for IVF.[8] Secondary surgical procedures for either of the above result in approximately 10% pregnancy rates over the ensuing six years.[8] IVF is a less expensive and more effective treatment modality than is a second surgical procedure.

Indeed some patients with severe tubal or adhesive disease may be best served by direct referral for IVF. For example, patients with both proximal and distal tubal disease have a pregnancy rate after surgical therapy that approaches zero, and Hulka[9] has pointed out that in the presence of distal occlusion similar results are obtained when more than half of the ovarian surfaces are obscured by adhesive disease. These patients, therefore, might best be considered for IVF without an attempt at surgical correction. Patients with severe endometriosis and extensive adhesive disease respond poorly to surgical and/or medical treatment and might appropriately be considered for IVF if a total of one ovarian surface is visible at laparoscopy. Pregnancies are rare in patients with long-standing (5 years or more) infertility due to oligospermia or multiple factor infertility, and these patients likewise are appropriate candidates for IVF. Patients with unexplained infertility seem to respond well to IVF.[2] It is of importance that referral be made without undue delay, since the pregnancy rate in patients undergoing IVF appears to decline after age 40.

IVF and embryo transfer have had a major impact on the surgical management of benign diseases in the female pelvis. In the recent past, most gynecologists recommended hysterectomy when salpingectomy was required in patients with chronic pelvic inflammatory disease, a practice which is clearly in error in 1985 except in emergency circumstances. When the tubes must be removed in a young, especially nulliparous, woman, every effort should be made to preserve the uterus and all possible ovarian tissue for future IVF. Indeed, even if both tubes and ovaries must be removed, consideration should be given to salvaging the uterus, since at least two live births have been reported from cryopreserved donor embryos from unrelated couples.[10] With further improvements in the primary pregnancy rates and in cryopreservation techniques, donor embryos may become available to larger numbers of women.

The advent and rapid development of IVF and embryo transfer have had a major impact on the management of infertile couples and on the surgical management of benign pelvic abnormalities in young women. The impact of these techniques will become even more profound as pregnancy rates improve and as cryopreservation of human embryos becomes a more generally accepted reality.

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I requested the following information which I felt would make the paper more useful to doctor and patient:

1. *Names and telephone numbers of persons in charge:*
   Director, Luther M. Talbert, M.D. *–966-5438*
   Nurse Coordinator, Linda Bailey, R.N. *–966-1150*
2. *For new appointments* *–966-4459*

3. *Waiting time from the initial visit to a treatment cycle is three to six months.*
4. *Cost — The present charges for a cycle of IVF at NCMH is $3700.00. This is a comprehensive fee which covers both professional and hospital charges. Most patients are reimbursed for half or more of the cost of IVF by their respective insurance carriers. Indeed, some companies pay in full. Because of the great variation in the policies of various insurance policies, prospective patients should check with their own insurance carriers. If either the physician or the patient requires assistance in dealing with the insurance company, they may contact the clinic Financial Counselor, Ms. Rita Brantley at 966-2131.*

EAS

SCIENTIFIC ARTICLE

Provocative Exercise Testing: A New Role for Cardiac Rehabilitation

Charles L. Baird, Jr., M.D.

- *A study of 121 patients at the Virginia Heart Institute between 1976 and 1982.*

EXERCISE testing is widely accepted for diagnostic and prognostic purposes in the management of ischemic heart disease. However, its role in the serial evaluation of therapeutic intervention has been limited due to cost, inconvenience and the failure to appreciate the necessity for objective pharmacologic control of myocardial ischemia. The cardiac rehabilitation program at the Virginia Heart Institute was modified to include nursing-supervised provocative exercise testing as a method of selecting therapy. Those patients whose exercise-induced myocardial ischemia could not be reversed pharmacologically or whose exercise performances were complicated by fatigue, hypotension or drug intolerance were considered for surgical intervention. The experience of the Virginia Heart Institute from 1976 to 1982 and the provision of provocative exercise testing during a six-week cardiac rehabilitation program are presented.

Methods

Patients with angina pectoris referred to the Virginia Heart Institute for outpatient rehabilitation underwent risk stratification prior to entering the program utilizing noninvasive and invasive methodologies. Those patients with unstable angina, intractable arrhythmias, congestive heart failure or left main coronary artery disease were excluded.

The exercise laboratory consisted of four electrocardiographically monitored stations. The six week program consisted of three 30-minute exercise sessions per week and involved both upper and lower extremity exercise. The nursing-supervised graded exercise test was symptom limited and consisted of ten minute bicycle exercise periods with initially low work loads. The exercise test terminated if the patient developed severe chest discomfort, arrhythmias or hypotension. Blood pressure, pulse rate and double product were correlated with electrocardiographic changes at 0, 5 and 10 minutes of exercise and were recorded for comparative purposes.

Three initial periods were utilized to establish a data base prior to drug intervention. Drug titration was initiated generally with a single drug in order to obtain maximum response and to minimize spontaneous variability. Weekly staff conferences were held with the nursing staff to review the patients' responses to drug intervention during the periods of provocative exercise testing.

Results

One hundred and fifty patients underwent cardiac rehabilitation with provocative exercise testing between 1976 and 1982. This group included 127 patients with ischemic heart disease and 23 with non-ischemic heart disease. Outpatient cardiac catheterization using the Sones technique was performed on 95% of the patients with ischemic heart disease (121/127); 22% (5/23) of those patients with non-ischemic heart disease required cardiac catheterization for

From the Virginia Heart Institute, Richmond, VA 23221.

Table 1
Patient Distribution

Ischemic Heart Disease	121 Patients	100%
Pre-event, angina without M.I.	70	58%
Angina post M.I.	25	21%
Angina post aorto-coronary bypass	10	8%
Post M.I.	7	6%
Post aorto-coronary bypass surgery	9	7%

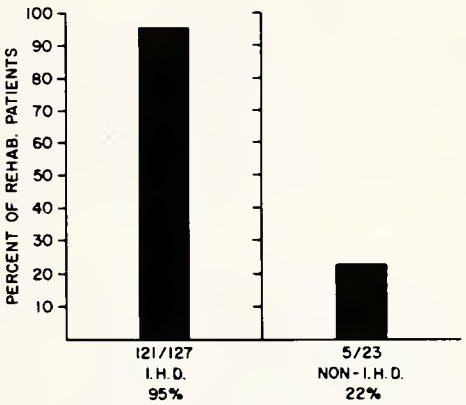


Figure 1. Catheterization procedures performed between 1976 and 1982 on Virginia Heart Institute rehabilitation patients. Patients with ischemic heart disease (I.H.D.) are on the left; non ischemic heart disease (NON-I.H.D.) are on the right.

further clarification (figure 1). Table 1 clinically classifies the 121 patients with ischemic heart disease.

Figure 2 provides the coronary angiographic data in patients with greater than 50% luminal narrowing.

Fifteen percent of our patients required surgery (18/121) at the end of the six-week program (figure 3). Three of these patients had single vessel disease, five had two vessel disease, and 10 had three vessel disease (figure 4). Medical management was considered successful in 85% (103/121) of the patients undergoing a drug intervention rehabilitation program.

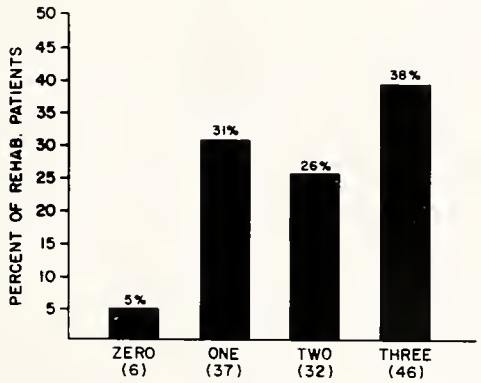


Figure 2. Distribution of coronary artery disease among 121 patients in the study. Six patients (5%) had no coronary artery disease; 37 (31%) had disease of one vessel; 32 (26%) had disease of two vessels; and 46 (38%) had disease of all three coronary arteries.

Discussion

The incorporation of provocative exercise testing into cardiac rehabilitation integrates monitored pharmacologic intervention into the accepted protocol of exercise therapy, psychosocial support and risk factor modification. This broadens the responsibility of cardiac rehabilitation and allows an active role for cardiac nurses in the application of drug therapy utilizing serial provocative exercise testing in the management of patients with ischemic heart disease who are potentially at high risk. The prognostic value of exercise testing in the prediction of survival in patients with coronary arterial disease has been previously documented.[1] Moreover, those patients who demonstrated reduced duration of exercise, hypotension or cardiac arrhythmias were identified as high risk for sudden death.[2]

Those patients who continued to exhibit exercise-induced myocardial ischemia unresponsive to maximal drug intervention or whose exercise periods were complicated by arrhythmias, hypotension or limited exercise performance were considered at increased risk and referred for surgical intervention. Conversely, those patients who demonstrated improvement during exercise testing were considered at low risk and advised to maintain medical intervention even when multi-vessel disease existed.

The recently published Coronary Artery Surgery Study demonstrated that the medical and surgical mortality rates were the same in a randomized study of 780 patients with stable angina pectoris.[3] This study supports the unreliability of coronary arteriography alone in providing a complete prognosis. The Virginia Heart Institute's retrospective analysis of 121 patients with ischemic heart disease further suggests a benign course even in those patients with three-vessel involvement (figure 3). Less than 20% of the patients evaluated at the Virginia Heart Institute failed to demonstrate reversibility of exercise-induced myocardial ischemia and were referred for myocardial revascularization.

Silent myocardial ischemia is responsible for 1200 unexpected sudden deaths daily in the United States. This problem led to the development of ambulatory cardiovascular

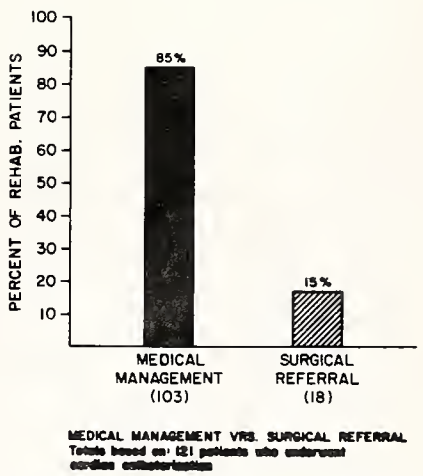


Figure 3. Eighteen patients (15%) were referred for surgical therapy; the remaining 103 (85%) were managed medically.

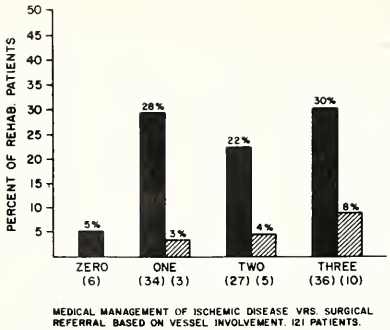


Figure 4. Treatment choices in the 121 patients according to the number of coronary arteries involved in their disease. Among those referred for surgery (18), three had one vessel, five had two vessel, and ten had three vessel disease. Among those managed medically, six had no coronary arteries involved, 34 had one vessel, 27 had two vessel, and 36 had three vessel disease.

screening with outpatient coronary arteriography at the Virginia Heart Institute in 1972.[4, 5] The recognition of significant coronary obstructive disease in a minimally symptomatic population led to the incorporation of drug intervention in the cardiac rehabilitation program which was initiated in 1976. The role of early detection at the Virginia Heart Institute is documented in this study since 58% of the patients entering the cardiac rehabilitation program had never experienced a myocardial infarction (table 1). The provocative exercise testing program not only affords the opportunity of selected treatment but also maximizes the use of risk factor modification, exercise conditioning and the drug stabilization which should be beneficial even in those patients referred for surgical intervention. The present epidemic of sudden death associated with multi-vessel disease, left ventricular dysfunction and complex ventricular arrhythmias has not been widely appreciated.[6] The continued reliance on subjective complaints by physicians tends to ignore the need for risk stratification based upon angiography and assessment of left ventricular function as well as arrhythmia analysis.

There is an urgent need to challenge the present health care system that has been unresponsive to the problem of sudden death. An alternative that deserves consideration is the development of ambulatory drug intervention interfaced with cardiac rehabilitation programs. Eventual acceptance by the medical community will require the recognition of serial exercise testing as a cost effective method of providing pharmacotherapy in the high risk population.

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Aquarius Redux — Lysergic Acid Diethylamide

Ronald B. Mack, M.D.

• *In which "trip" is redefined, again. Caveat emptor.*

"WHEN the moon is in the seventh house and Jupiter aligns with Mars, then peace will guide the planet and love will steer the stars." Surely you remember this refrain from the ever-popular tune, "The Age of Aquarius," from the smash-hit stage sensation, "Hair." Seeing these words should bring back into consciousness the smell of incense, the turbulence between the youth and Establishment, the long hair, the "funny clothes," the "funny" cigarettes, miniskirts, and of course LSD — the drug of peace and love, brother. There is some evidence that there might be a resurgence of this rather "base" acid in this country among the incompletely formed in our culture — the adolescents. The use of LSD continues a decline noted three or four years ago but there are data to show that in some areas of America there has been a resurgence. In a recent statement the Drug Enforcement Agency alleges that a slight increase in the use of LSD is evident. It is always of interest to see our young people repudiate their parents' generation by emulating them as they were — my sons now have short haircuts and I do not; my boys wear three-piece suits and wing tip shoes to work and I don't. We do agree on at least one thing, however — LSD is a chemical trip that no one needs to take. The DEA alleges that the resurgence may be due to the fact that PCP (Angel dust) has such a bad reputation now that users are switching back to LSD.

LSD-25 remains the most potent and abused hallucinogen. Its discovery, as in so many medical breakthroughs, was by accident. Scientists in Switzerland were searching for pharmacologically useful products of ergot. Ergot is a fungus, a parasite of the rye grain. "Ergotism" has been known since the Middle Ages and the acquisition of this substance by the unwary produced convulsions and hallucination and was subsequently given the eponym St. Anthony's Fire. So here was this Swiss chemist in 1943 working with ergot alkaloids in the lysergic amide series who found that the 25th preparation (LSD-25), when ingested by the chemist, caused hallucinations.[1] It was even considered, during World War II, as a potential incapacitating agent in warfare. After WWII, LSD research was present in our country where supposedly it was used on emotionally ill patients in an effort to discern the biochemical nature, if any, of such illnesses. With the advent of strict Federal control, the use of LSD in such experiments dropped off remarkably.

From all of this followed the illicit use of this drug and the rest is history. Who can forget Timothy Leary, Ken Kesey, acid rock, *L*ucy in the *S*ky with *D*iamonds, etc.? What is it about this drug that so intrigues the user and makes "dropping acid" so cool? The users allege that at the very least LSD produces a "consciousness-expanding" experience, AKA a psychedelic experience. Of course there can be a wide variation in user response but a not unusual scenario goes something like this: initially, because LSD is rapidly absorbed from the GI tract, there can be noted, within 30-40 minutes of ingestion, marked mydriasis, conjunctival injection, salivation, cutaneous flushing, trembling, rapid pulse. (When was the last time you felt that way? When your secretary said that Mike Wallace and the 60 Minutes crew was in your waiting room?)

This initial, rather peculiar physical reaction is then followed by the real action, the "trip." Here the user feels depersonalized, with a loss of body image and decreased sense of reality. One of the most characteristic experiences reported by psychedelic drug users is the phenomenon of *synesthesia*, i.e., the translation of one sensory experience into another sense organ, e.g., "smelling" colors, "seeing" music — certainly, colors described as more vivid, and visual distortions with very altered perceptions of color, time and distance are typical. Hearing becomes very, very acute. Apparently external sounds such as music combine with the distorted imagery to enhance synesthesia. The sense of smell becomes remarkably intense and the presence of incense or flowers and music are part of the ritual.

The initial physical reaction lasts for a few hours whereas the psychic "trip" can last for 8 to 12 hours. At the peak of this psychedelic experience it is alleged that there is a feeling of rebirth and transcendence[1] — a feeling of oneness, compassion, tolerance and love for all things. After the peak is reached and the "tripper" re-enters, there is a gradual coming back to the "self" and to the environment. After such a voyage to unreality the passenger can recall details of the encounter. Now does that sound like a good time to you? Remember this is the desired effect; this is a good trip. The last time I felt this way was during a dream when I was called upon to do camp physicals on the Dallas Cowboy Cheerleaders. Some authors suggest that LSD affects the hypothalamus and therefore serotonin metabolism. Serotonin is supposedly one of the neurotransmitters that regulates or censors the flow of information transferred at nerve cell synapses. By blocking or antagonizing serotonin, LSD allows the "inner and outer world contents to stream into the brain."[1]

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

A "bad trip" can be scary indeed — it consists of an acute panic reaction with feelings of identity loss and/or a disintegration into nothingness or a feeling that there is no reality. The patient can have very frightening illusions or delusions with real honest-to-goodness marrow-shaking true hallucinations. "Bad trips" seem to be more common among neophyte experimenters and people who take very large doses of this delightful fungus derivative. If a pre-school child gets into this stuff accidentally the situation may be hard to diagnose — be sure to include accidental LSD ingestion in your differential diagnosis of a severe, acute panic reaction (you mean like the three-year-old out there in the clinic today who was told that he needed some "shots" in order to get into nursery school and who got so "freaked out" that his screams shattered the glass on all the otoscopes and whose bouncing off the walls caused your diplomas to fall off the wall?). Prolonged psychotic behavior following LSD use can also occur and closely resembles paranoid schizophrenia. It should be mentioned that LSD can't be taken continuously and still reproduce its psychedelic potential day after day; tolerance develops quite quickly and in order to regain the possibility of having a pleasant voyage the serious traveler needs to abstain for at least a few days.

Some word should be mentioned about this drug's physical descriptions as found on the street. LSD is cheap to make but apparently it is most frequently imported from foreign "connections." The drug is available in capsules, as a powder, in solution, as a tablet on a piece of lump sugar, impregnated into gelatin squares (known as "window panes") or blotter paper (known as "blotter acid"). Recently I received the following notice from a nearby elementary school: "To All Concerned Parents With Unsuspecting Children: A form of tattoo called 'Blue Star' is readily available in some areas of the U.S. It is a small sheet of white paper containing 'blue stars' the size of pencil erasers. Each star is saturated with LSD. Absorption can occur through licking the star or just handling the paper. There are also brightly-colored tabs the size of postage stamps which have pictures of Superman, Mickey Mouse, other Disney characters, etc. and so on." Think of this: an ounce of uncut LSD can provide 150,000 "hits" of 200 μg each; 35 μg or more can cause "hallucinations" and the usual dose on the street is 150-200 μg. Apparently most LSD sold on the street is really LSD. However, it is alleged that a fair amount of LSD is laced with PCP. You can take LSD into your body any way you wish but per os is the usual way to go.

The treatment of LSD "intoxication" really is restricted to the unfortunate "acid-dropper" who undergoes a "bummer" (AKA "bad trip") — the acute panic reaction — or to an innocent pre-school or older victim who gets the drug by mistake. People on "good trips" generally do not come to visit you in the emergency room. It is usually too late to attempt gastrointestinal decontamination and of course there is no antidote. The essential treatment for a "bad trip" is to "talk him/her down," to establish for the patient the link to reality. To try to do this in a busy emergency room may not be a good idea for the presence of the white coats, other patients, telephones ringing, beepers going off, and the incessant noise often exacerbate the hallucinations. A quiet non-threatening room is more suitable whereby you can re-introduce to the patient the "real" world slowly and positively. Chlorpromazine (Thorazine) has been a time-honored suggestion for relief of the panic but this drug can cause hypotension and severe cardiovascular collapse and is best avoided. The benzodiazepines, e.g., diazepam, are preferred by many authorities as a safe, efficient therapeutic modality if you need to use a drug at all. Still, the essential treatment consists of a guide or leader to talk the patient back into the less weird world that we live in.

Currently I am working on a series of experiments in which I have discovered the presence of love receptors on the heart. I have named them *lambda* receptors. There are several types, such a lambda$_1$, lambda$_2$, etc. These love receptors can change frequently in response to many variables and, we have discovered, are in some ways age-dependent. For example in the first 6 months of life an infant only produces a limited supply of lambda receptors with agonists with a fairly long half-life (T½) and which are directed towards the self. At 6-8 months of age the infant also develops love receptors for its mother and if the mother leaves the child's visual presence for any period the infant cries and this is referred to as separation anxiety. The ramifications of these experiments seem almost limitless and I am grateful to my department chairman for his encouragement and help in obtaining a grant for this work.

Such examples of how love receptors function include: the people who fall in and out of love quickly have lambda$_1$ receptors with a very short T½; people who remain happily married for 40 or 50 years obviously have love receptors with a very long T½ and so on. Our work suggests, after meticulous experiments, that aphrodisiacs are probably lambda$_2$ agonists. (We have not found one yet that really works.) Other agonists, false transmitters actually, include perfume for women or aftershave lotion for men, money, fur coats, sumptuous meals, etc. Furthermore, we have discovered that certain human characteristics can reduce the T½ of these love receptors — examples include halitosis, love affairs outside of the current love relationship, persistent nocturnal headaches, etc. As you might imagine, congenital absence of a lambda receptor also occurs, often resulting in spinsterhood, bachelorhood, etc.

One exciting experiment, finished just this past month, demonstrates that love for a grandchild causes a remarkable increase in lambda$_3$ receptors with the longest half-lives discovered to date. We plan in the future to investigate lambda agonists that have even longer T½s and that are not dialyzable. There seem to be enough lambda blockers at this time.

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A Checklist of Practice Marketing Ideas

Leif C. Beck and Patricia M. Salmon

• *A brief outline of ideas for marketing your practice.*

ARTICLES on marketing tend to miss their mark when directed to practicing physicians. Many of the articles seem directed to broad principles which doctor-readers find just do not reach the realities of their practices. Others present so many self-evident points that they fail to give the physicians much to work with.

As consultants to medical practices, we recognize both the importance of the marketing topic and the difficulty in properly translating it for practitioners. Hence, this "semi-outline" is presented as a variation in form intended to help doctors to get hold of the ideas.

Marketing is an attempt to anticipate and/or shape consumer behavior. To do that effectively, a practice must determine what patients want or need as well as what motivates their choices in health care. It must then develop strategies and routines either to adapt the practice to the consumer's needs and/or expectations or to reeducate patients regarding health care choices. The goals would be to make the particular practice most appealing as a health care provider.

Though this is no easy task, it can be accomplished with careful analysis and planning, followed by a variety of specific steps. The process involves the following:

I. Practice Assessment

The obvious benefit of assessing a practice is to identify its pluses and minuses. Practice assessment, however, provides a variety of other benefits:

- It gives the practice an opportunity to lay the groundwork for developing marketing strategy.
- It provides the practice with direction and thus offers it an opportunity to shape its future rather than just letting it develop by chance.
- It helps the practice and its people use their time, resources and skills most efficiently and to their best advantages.
- It helps the practice deliver a better level of patient care.

There are two components of practice assessment: internal assessment and external assessment. Let us describe each.

A. Internal Assessment

(1) *Developing a patient profile.* To accomplish this, a practice must analyze its patient mix. This includes gathering information on those people (i.e., age, occupation, marital status, insurance coverage and the like) along with their opinions and attitudes on such matters as:

- Do the patients understand the specialty?
- What do they think of the physical facility?
- Are they satisfied with the health information they receive?
- Why are they seeking treatment?
- Do they want additional services that the practice does not provide?

This information can be obtained through fairly simple research and the use of patient questionnaires.

(2) *Assessing the staff.* This should include considering how an office's employees empathize with the patients. Do they understand this part of their job? How do they handle patients' questions as well as patients' complaints? Do they complement or detract from the doctor's or doctors' personalities and styles?

In advising physicians about marketing, we often point out that they should not spend much on marketing routines if their own "house" is not in order. Grumpy staff, long waits, constantly busy phone lines, unattractive offices and the like are all involved in patients' choices when seeking health care.

One obvious source of information about staff is careful observation. Additionally, patient questionnaires will often tell much about the quality and personality of an office's personnel.

Physicians should also pay close attention to patients' comments about the employees, even those seemingly said in jest. Those casual comments often say much more than we realize.

(3) *The self assessment.* The physician must put into writing some critical evaluations of himself or herself, and a group practice should do this for its physicians both individually and collectively. Important questions include:

- How does the physician rate his/her interpersonal skills?
- What are his/her major strengths or weaknesses as a physician?
- Is the doctor(s) satisfied with the type of patients being seen?

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From the Health Care Group, 400 GSB Building, Bala Cynwyd, PA 19004.

- Are there other types of patients he/she would prefer to see?
- What are the doctor's personal goals and ambitions?

(4) *Assessment of office facility*. This would include considering whether the waiting room and reception area are comfortable and clean. Does the practice offer areas of patient confidentiality for billing problems or surgical scheduling? Does the facility reflect positively on the practice? Does it project the image the physician(s) desire? Is it accessible and easy to find?

Again, these items can be considered through observation as well as through solicited or unsolicited patient comments and patient questionnaires.

(5) *Assessment of the practice's clinical services*. This would include whether the range of services offered is compatible with specialty type; are there other services that could be provided to improve the practice? What would be the cost of adding these services, and would they be useful to the patients and profitable to the practice?

B. External Assessment.

(1) *Assessment of competition*. It is important to identify a practice's "competitors." What does the doctor know about them? Is the practice losing patients to them? Is it gaining patients from them? Is the competition increasing, decreasing or stable?

Information on other practices, though partly known just by involvement, can also be obtained through the Yellow Pages, patient surveys, ex-patient surveys, pharmaceutical representatives and the like.

(2) *Assessment of demographics*. This includes considering the service area's breakdown by age, sex, race, household size and so forth. Is the service area's population increasing or decreasing? Are there any important changes taking place in the area demographics?

Not every marketing idea works for the entire population. On the basis of demographics, a doctor might thus want to identify certain target areas with the most potential for successfully implementing its goals. As an oversimplified example, a geriatric practice would probably not seek out an area where the average age is 26, where the elementary school system has shown significant growth, etc.

(3) *Assessment of local business and economic environment*. What are the trends in employment? What types of businesses are moving into the practice area and the surrounding communities? Are there any newly developing plans as to local transportation, public utilities, zoning changes and the like?

(4) *Assessment of area's epidemiological environment*. This might include identifying the frequencies of disease and illnesses in the service area. Are there any concentrations of industry in the area that might contribute to the incidence of certain diseases or illnesses?

(5) *Assessment of social/cultural and legal/technological trends*. How might these affect the practice's future?

Much like internal assessment, the external assessment provides a means of identifying potential opportunities, needs and constraints. Both processes are a key part in developing the practice's objectives and adopting a business plan.

II. Developing a Business/Marketing Plan

With the supply and demand for health care providers radically changing, doctors should be aware of the changes and the long and short range effects on their practices. Mapping long and short term goals and constantly monitoring progress toward them will give doctors the best opportunity to accomplish the goals.

A business/marketing plan is a practice blueprint for the future. It allows a doctor to logically decide how he will in the future most satisfactorily provide his or her services and to efficiently allocate resources to accomplish those goals.

Suppose, for example, a cardiologist is in an area where the number of cardiologists is greater than can realistically be supported by the patient volume. It is thus essential that this doctor identify what he can offer to patients as well as what potential patients he should offer it to in order to make his practice different and more attractive than the others in the area.

Assessing the practice internally and externally, taking advantage of the strengths and eliminating or covering up the weaknesses and knowing and attempting to reach the largest potential patient population would help his practice compete well. In fact, real application to the effort could even put him in position to be a "premier" practice.

Once this doctor has determined his preliminary goals and objectives, studied and analyzed the local demographic statistics and trends, studied and analyzed the competition, evaluated his strengths and weaknesses, identified some opportunities on which to capitalize, he should have his plan in writing to act as a roadmap for the months and years ahead.

III. Marketing/Promotion Ideas

Once one had developed the plan, there may be many steps directed to actually reaching out to existing and potential patients. Without extending to the more "progressive" plays such as advertising, here is a list of steps to consider:

- Non-traditional office hours, such as evenings, mornings and/or weekends. Depending upon the age of one's patient population, patients may either be working or in need of rides that are more easily obtainable at less traditional times.
- Add additional services that allow the practice to offer "one-stop shopping," so to speak. For our cardiologist example, this might include stress testing, cardiac rehabilitation programs and nutrition counseling in his own facility for cardiac patients.
- A physician with an elderly patient population might consider assigning one person in his or her office to spend time "training" patients about their Medicare claims and how they should file them (depending upon the practice's policy under the new fee freeze). It is often particularly confusing for some senior citizens, and they tend to appreciate any help offices can give. Small brochures about the steps involved in filing Medicare forms for reimbursement are also popular.
- Depending upon the area's demographics, a physician might consider opening a satellite office to target another part of the area not now serviced by his colleagues. This doctor's accessibility might cause that area's patients to

start visiting him.

- Patient education information is important for any practice. Though it might be available through professional societies and/or drug companies, having it personalized with the practice's name is both a valuable marketing tool and a service to the patient.
- If the practice does not have one already, it should develop a Patient Information Booklet to provide a handy reference as to office policies and procedures. While usually helping save staff time, it is an excellent marketing tool as patients pass it on to friends.
- The use of patient newsletters is also an excellent marketing, as well as educational, tool. We see a wide variety of such newsletters with news about practice and patient activities, health informational columns, etc. A newsletter provides a service to patients while spreading the doctor's name and reputation.
- Involvement in community activities, such as lectures to senior citizens and other groups, is a traditional way for physicians to get their names out. It is still among the most successful practice-builders.
- Involvement with local industry might target larger blocks of patients, especially if contract relations with some employers can be worked out.
- Letters to referring doctors following patient visits are frequently taken for granted, but they are necessary marketing tools. A "marketing-oriented" doctor will handle the reporting obligation with special attention to the referrer's satisfaction.
- And some specialists send their referring doctors monthly or quarterly letters updating them on new findings in the specialty, new services available and whatever else will remind those referrers of the senders.

IV. Conclusion

We hope this low key discussion of marketing ideas as they might apply to a practicing physician will be useful. By reviewing our casual outline as though it were a checklist, those ideas might have more chance of actually being pursued than is typically the case.

LEARNING EXPERIENCES FROM UNC

Lest We Forget — Spring Is Here: North Carolina Spotless Fever in Adults

William B. Blythe, M.D.

SUMMER is coming, and Variety Vacationland once again will be alive with an abundance of outdoor activities: camping, hiking, strolling, and frolicking in the woods; gardening; picnicking; barbecuing under the trees; and lolling on the lawn.

Ah, Summer!

But wait! All is not sweetness and fun. The wood tick and dog tick, of which 3-5% are carrying Rickettsia Rickettsii, will also be aestivating outdoors among us. Thus, the specter of Rocky Mountain Spotted Fever will be hovering over the good physicians, reminding them that this disease is most prevalent in North Carolina from April through October.

Recently, Dr. Janet Fischer, a keen observer of Rocky Mountain Spotted Fever in North Carolina for over three decades, suggested at Pearls Day in Chapel Hill that North Carolina Spotless Fever may be a more appropriate name for Rocky Mountain Spotted Fever in *adults*.

From the Division of Nephrology, Old Clinic Building 226H, UNC, Chapel Hill 27514.

This is her reasoning: approximately 64% of adult patients with Rocky Mountain Fever who do not demonstrate the much-emphasized rash die in spite of the availability of effective therapy and the fact that treatment on or before the fifth day of clinical disease almost always results in recovery. This appalling death rate in rash-free adults is a consequence of the physician not considering the correct diagnosis early enough.

It is Dr. Fischer's belief that this occurs largely because of two factors: 1) The adjective "spotted" is misleading. About 10% of adults never develop a rash and, in 20% more, the rash does not develop until the second week of the disease when complications and death are more apt to occur. 2) "Rocky Mountain" is also a misnomer and tends to obscure the fact that more cases of Rocky Mountain Spotted Fever are reported annually in North Carolina than any other state.

The only part of the name that accurately portrays the disease in adults in North Carolina is "fever."

Dr. Fischer advocates that a five-day course of tetracycline be strongly considered by physicians when confronted by an adult patient with the following:



Camping, hiking, frolicking in the woods, picnicking, lolling on the lawn: beware the ticks.

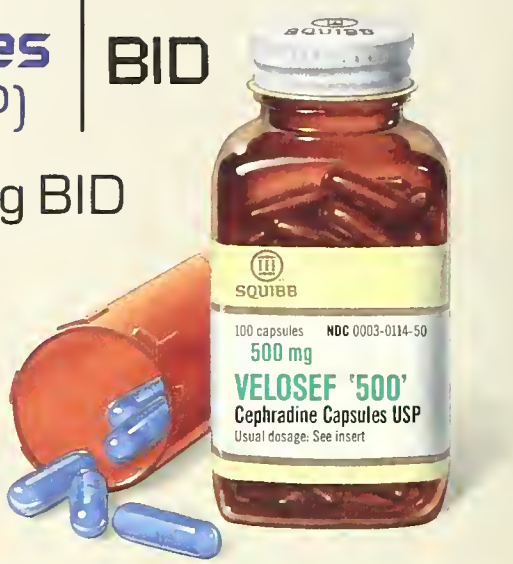
1) an illness lasting for more than three days and getting worse.
2) a normal white blood cell count with a shift to the left in the differential count.
3) a severe headache.
4) *evening* fever greater than 102°. (The temperature is frequently normal when the patient visits the physician.)
5) Thrombocytopenia.

Keep North Carolina Spotless Fever in mind this summer.

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- ☐ Five (5) First Prizes... a briefcase-size Hewlett-Packard Portable Computer valued at $3,900.00.
- ☐ 500 Second Prizes... a copy of *Computerizing Your Medical Office: A Guide for Physicians and Their Staffs* valued at $17.50

Just complete and return the attached reply card!

OFFICIAL RULES: "Computers in Health Care Drawing"
NO PURCHASE NECESSARY.
(1.) On an official entry form handprint your name, address and zip code. You may also enter by handprinting your name, address and zip code and the words "Velosef–Computers in Health Care" on a 3" x 5" piece of paper. Entry forms may not be mechanically reproduced. **(2.)** Enter as often as you wish, but each entry must be mailed separately to: "COMPUTERS IN HEALTH CARE DRAWING," P.O. Box 3036, Syosset, NY 11775. All entries must be received by September 9, 1985. **(3.) Winners will be selected in random drawings from among all entries received by the National Judging Institute, Inc., an independent judging organization whose decisions are final on all matters relating to this sweepstakes. All prizes will be awarded and winners notified by mail. Only one prize to an individual or household. Prizes are nontransferable and no substitutions or cash equivalents are allowed. Taxes, if any, are the responsibility of the individual winners. No responsibility is assumed for lost, misdirected or late mail. Winners may be asked to execute an affidavit of eligibility and release. (4.)** Sweepstakes open only to physicians residing in the U.S.A., except employees and their families of E.R. SQUIBB & SONS, INC., its affiliates, subsidiaries, advertising agencies, and Don Jagoda Associates, Inc. This offer is void wherever prohibited, and subject to all federal, state and local laws. **(5.) For a list of major prize winners, send a stamped, self-addressed envelope to: "COMPUTERS IN HEALTH CARE" WINNERS LIST, P.O. Box 3154, Syosset, NY 11775.**

VELOSEF® CAPSULES
Cephradine Capsules USP

VELOSEF® FOR ORAL SUSPENSION
Cephradine for Oral Suspension USP

DESCRIPTION: Velosel '250' Capsules and Velosel '500' Capsules (Cephradine Capsules USP) provide 250 mg and 500 mg cephradine, respectively, per capsule. Velosel '125' for Oral Suspension and Velosel '250' for Oral Suspension (Cephradine for Oral Suspension USP) after constitution provide 125 and 250 mg cephradine, respectively, per 5 ml teaspoonful.

INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae*) and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosel (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae*, staphylococci, and *S. pneumoniae*; Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli*, *P. mirabilis*, *Klebsiella* species, and enterococci (*S. faecalis*).

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS: *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

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Diuretics (potent "loop diuretics," e.g., furosemide and ethacrynic acid) — Enhanced possibility for renal toxicity.

Probenecid — Increased and prolonged blood levels of cephalosporins, resulting in increased risk of nephrotoxicity.

Drug/Laboratory Test Interactions: After treatment with cephradine, a false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®. False-positive Coombs test results may occur in newborns whose mothers received a cephalosporin prior to delivery. Cephalosporins have been reported to cause false-positive reactions in tests for urinary proteins which use sulfosalicylic acid, false elevations of urinary 17-ketosteroid values, and prolonged prothrombin times.

Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers: Since cephradine is excreted in breast milk during lactation, exercise caution when administering cephradine to a nursing woman.

Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Hematologic — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structure infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h). For dosage recommendations in patients with impaired renal function, consult package insert.

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae*: 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

For full prescribing information, consult package insert.

HOW SUPPLIED: 250 mg and 500 mg capsules in bottles of 24 and 100 and Unimatic® unit-dose packs of 100. 125 mg and 250 mg for oral suspension in bottles of 100 ml and 200 ml.

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785-501 Issued: Jan. 1985

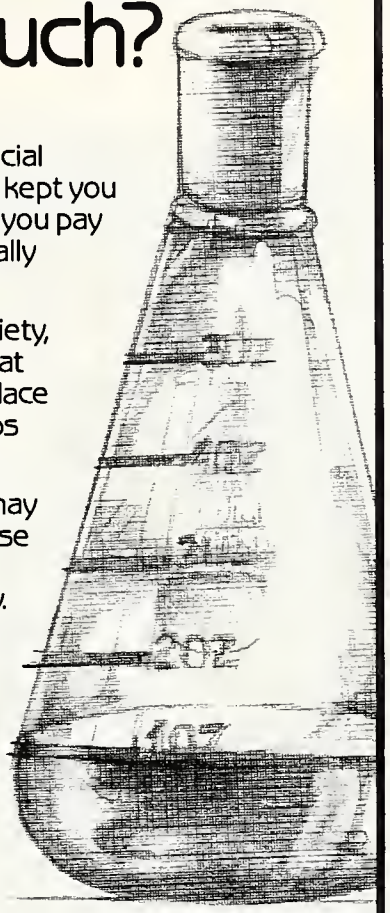
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For further information about Charter Hills or admission procedures, contact:

Medical Director:
William R. Bodner, Jr., M.D.
Hospital Administrator: Harold Small

Charter Mandala Hospital

3637 Old Vineyard Road
Winston-Salem, North Carolina 27104
(919) 768-7710

Beds: 72
Psychiatric Staff: 12
Programs: Adult and Adolescent Psychiatric; Adult and Adolescent Addictive Disease

For further information about Charter Mandala or admission procedures, contact:

Medical Director: Bruce W. Rau, M.D.
Hospital Administrator: Harold Small

Charter Pines Hospital

3621 Randolph Road
Charlotte, North Carolina 28211
(704) 365-5368

Beds: 60
Programs: Adult and Young Adult Psychiatric

Scheduled to open in February 1985

For further information about Charter Pines contact:

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R.Gordon Crandall, M.D.
Hospital Administrator: Stan Hilliard

Charter Northridge Hospital

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Programs: Adult and Adolescent Addictive Disease

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September 17, 1985 at 7:00 p.m. Mountain AHEC *(Lecture Hall)*	Asheville
September 24, 1985 at 7:00 p.m. East Carolina University, School of Medicine *(Brody Auditorium)*	Greenville
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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test;[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

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THE BALANCED CALCIUM CHANNEL BLOCKER

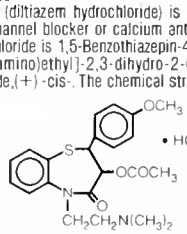
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PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered.

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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North Carolina Medical Journal

Features for Patients June 1985

The Impact of AIDS on Blood Donation

Jerry E. Squires, Ph.D., M.D.

In 1978 ond 1979 several haspitols in New York ond Los Angeles recagnized a syndrome of opportunistic infections in previausly healthy young adult patients. The infections most frequently noted included Pneumocystic pneumania, Candido esophogitis, disseminoted cytomegalovirus and disseminated Myocobacterium ovium-intracellulore. Epidemiologic investigotion of these patients reveoled that almost all were male homosexuals or bisexuols or parenteral drug abusers. At about the same time a similar population of previously healthy young men were recognized who developed an unusuolly aggressive form of Kaposi's sarcomo. Priar to this time Kaposi's sarcoma was most commonly described as o relatively slow-growing, locally invasive neoplasm of elderly men. The more aggressive form hod been seen anly in certoin immunodeficient patients.

Laboratory evoluatian af these potients demonstroted a profound defect in cell-medioted immunity accompanied by a relatively intoct humoral immunity. The impaired cellular immune function was manifest in several ways, including: (1) anergy (lock of response) ta multiple skin test challenges with ontigens such as Candida, mumps, tetanus, etc., (2) lymphopenia (decreased proportion of lymphocytes in the blood), with mony patients having fewer than 500 lymphocytes/mm,^{3} (3) decreased numbers of T-lymphacytes while numbers of B-lymphacytes were relotively normol, and (4) a severe deficiency of "helper" cells and on increosed number of "suppressor" cells.

Since 1978 additional patients have been described who demanstrate the combination of opportunistic infections, Kaposi's sarcoma, an acquired severe deficiency af the cellulor immune system and o lifestyle including homasexuality, bisexuality, ar intravenous drug abuse. The term ocquired immune deficiency syndrome (AIDS) hos been most cammonly opplied to this complex of findings.

Eorly studies of lorge numbers of patients suggested that AIDS was most commonly transmitted thraugh intimate sexuol contact. However, the presence of AIDS in intravenous drug abusers initially suggested that an infectious agent might be transmitted parenterally (by injection). Subsequent documentotion af AIDS in hemaphiliacs as well os both odult and pediotric patients receiving blood transfusians have confirmed this mode of transmission. As cases have accumulated during the post four yeors, relotively well defined risk groups have emerged. As of February 1985, 8495 cases of AIDS hove been recarded by the Centers far Disease Control (CDC). Of these, 73% hove been homosexual or bisexual men; an additional 17% are introvenous drug users. Only 1% (appraximately 100 cases) have been attributed to blood transfusion.

In spite of what oppeored to be o relatively smoll risk af developing AIDS following o blood transfusion, public anxiety about the safety of the blood supply demanded that oddi-tionol precoutions be taken. Therefore, in March 1983, the U. S. Public Heolth Service issued a recommendation thot members of groups at increased risk for AIDS should refrain from donating blood. In addition, the Food and Drug Administration recommended that all blood banks provide educational materials about AIDS to donors, and olter the medical histary taken on each donor to include questians concerning AIDS symptoms, such as night sweats, un-

From the Carolinos Region, American Red Cross, 2425 Park Rood, Chorlotte 28236.

explained fevers, unexpected weight loss, lymphadenopathy, and skin lesions. The effectiveness of these "interim guidelines" in reducing the risk of contracting AIDS following a blood transfusion is difficult to assess. It is important to realize, however, that during the past four years, while approximately 13 million patients received nearly 36 million units of blood and components, only 100 cases of post-transfusion AIDS have been reported.

In spite of the minimal risk of contracting AIDS through blood transfusion, public concern for the safety of the blood supply has been high, and a variety of demands have been placed upon the blood delivery system. One of the most complex of these was the question of **directed donations.** A directed donation is one in which the potential blood recipient selects his own blood donors from family, friends, co-workers or private donor clubs. Most blood donor centers have recommended that such directed donor programs not be established. The reason for the reluctance on the part of blood donor establishments to accept directed donations stems from two concerns: (1) the probable impairment of the volunteer donor system if large numbers of donors opt to withhold blood donation pending the need of a friend or family member, and (2) the probability that directed donations are actually *less* safe than the current voluntarily donated blood supply. The reason that these donations may, in fact, provide a less safe transfusion product results from the "social pressure" to donate blood for a friend or family member in spite of past medical history or lifestyle.

Another demand placed on blood banks due to the anxiety about AIDS resulted from a decrease in the numbers of potential donors. Some potential blood donors have been clearly confused by reports in the media. In a survey completed in 1983, 26% of 2000 adults polled nationwide believed that AIDS could be contracted by donating blood. This is clearly incorrect; nevertheless, the impact upon the blood supply in some areas of the country was significant.

The announcement in April 1984, that Dr. Robert Gallo of the National Cancer Institute had identified the probable cause of AIDS created new demands on blood banks. The virus implicated as the cause of AIDS is known as human T-lymphotropic virus-type III (HTLV-III). The association of this virus with the clinical syndrome of AIDS has, to some degree, been circumstantial, but the data are quite convincing. Evidence of the presence of HTLV-III was found in more than 90% of patients with AIDS; in addition, Gallo reported that each of ten blood donors whose recipients developed AIDS were found to have evidence of HTLV-III. Finally, chimpanzees experimentally infected with the HTLV-III virus developed enlarged lymph nodes similar to the lymphadenopathy that often precedes AIDS.

The development of a sensitive screening test for HTLV-III has been a major priority during the past year. Five companies were authorized by the Food and Drug Administration to adapt a test for antibodies to HTLV-III originally developed by the National Cancer Institute. The test itself is an enzyme-linked immunosorbent assay (ELISA) which uses viral antigens derived from whole disrupted HTLV-III. Antibody to HTLV-III has been found in 68-100% of patients with AIDS and in 84-100% of persons with an AIDS-related condition such as unexplained lymphadenopathy. On the other hand, fewer than 0.5% of individuals with no known risk for AIDS are reactive in the test for antibodies to HTLV-III. The sensitivity of the test has recently been reported to be greater than 96% while the specificity is generally considered to be greater than 97%.

The use of this ELISA test to screen donated blood for antibodies to HTLV-III should have been fully operational in most blood donor centers before May 1, 1985. At that time a variety of Public Health Service recommendations concerning the testing for antibodies to HTLV-III took effect. These recommendations affect the blood recipient, donor, and his physician in various ways.

The first of these recommendations suggests that all blood or plasma should be tested for HTLV-III antibody by the ELISA test and any found positive should be discarded. Clearly, the major impact of this recommendation will be upon the potential blood recipient. While the risk of acquiring AIDS through blood transfusion has been minimal, the use of this test should reduce that risk still further. Hopefully, this will restore the confidence of many potential blood recipients in the safety of the blood supply. The Public Health Service also recommends that potential blood donors be informed that their blood will be tested for antibody to HTLV-III. This notification should have begun on or about May 1, 1985. The impact of this notification on the willingness of donors to continue to donate is difficult to assess.

One of the most difficult recommendations concerns notifying donors who have positive tests for antibody to HTLV-III. While there is great concern about the psychological impact of this information, failure to provide the patient with such notification might inappropriately preclude medical evaluation and protection of sexual contacts. It will be imperative to make the patient aware that the significance of a positive test for antibodies to HTLV-III is uncertain. The limited information available on the natural history of the syndrome suggests that only 5-19% of seropositive homosexual men develop AIDS within 2-5 years; an additional 25% develop lymphadenopathy, oral candidiosis or other AIDS-associated condition. In an effort to minimize the risk of reporting false-positive results to the individual, each initially positive result will be repeated in duplicate; any repeatedly positive sample will also be submitted for confirmation testing. Currently, the confirmation test most commonly used is the

Western blot. The numbers of blood donors who will have confirmed positive test results is difficult to estimate. However, preliminary evaluation suggests that fewer than 0.03% of the donor population will have confirmed tests for antibody to HTLV-III.

Those few blood donors who are identified by the testing procedures will be contacted by a Red Cross physician or by a trained nurse and referred to appropriate doctors or clinics. Perhaps a more tangible concern is that members of certain groups at increased risk for AIDS will donate blood simply to determine if they carry the antibody to HTLV-III. The Public Health Service is handling this portion of the problem. Its program is described in some detail in the papers that follow.

AIDS Hotline
1/800/225-AIDS

AIDS Information for Doctors and Patients

J. N. MacCormack, M.D.

Alternate Sites for HTLV-III Antibody Testing

On March 2, 1985, Margaret Heckler, Secretary of Health and Human Services, announced that the FDA licensed the first commercial manufacturer to make and distribute test kits for the detection of antibodies to the HTLV-III virus. This has already been widely reported in the press. Blood banks have begun proficiency testing. During May, blood banks are expected to begin donor notification of test results. The State Laboratory is expected to have the kits available to begin performing the HTLV-III antibody test sometime in early May. The anticipated public health benefit of this overall program to protect the nation's blood supply has dictated the unusually rapid introduction of this test.

Alternate test sites will be necessary to discourage high-risk individuals such as male homosexuals and intravenous drug abusers from using the blood banks simply to be tested. Although the test is highly specific, there is the danger that some persons will have negative tests but harbor the virus, thereby allowing a donor to contaminate the blood supply. Local health departments will serve as alternate test sites for HTLV-III antibody testing, which will contribute to the goal of protecting our blood supply. None of us welcome the prospect of needing a transfusion, but the possibility becomes a greater concern unless everything possible has been done to insure the safety of that product.

Local health departments that become alternate test sites are expected to provide pre-test counseling, to draw and submit serum samples to the State Laboratory, and to conduct post-test counseling. The Sexually Transmitted Disease (STD) Branch will assist local health departments in establishing alternate test sites.

Local health department staff may not have the time or be able to answer all questions concerning HTLV-III antibody testing. In early May, the STD Control Program will install a toll-free Hotline (1-800-225-AIDS) to assist in answering questions or making referrals to support groups. Community mental health centers have been informed that local health departments may be referring individuals with positive test results.

General Guidelines for Alternate Test Sites

A. General responsibilities

1. *Provide pre-test counseling.*
   All patients should receive a "Pre-Test Information Sheet"; this should be discussed with the patient (see protocol for pre-test counseling).
2. *Draw serum and send to State Laboratory.*
   The State Laboratory protocol for specimen collection should be followed.
3. *Provide post-test counseling.*
   Patients with positive test results should be given the information sheet entitled "Information for those with a Positive HTLV-III Antibody Test." This should be reviewed with patient.

B. Availability of sites and scheduling

1. If a county health department has satellite clinics, it may be easier to decide to offer HTLV-III antibody tests at only one center. If more than one site will be used, inform the STD Control Program so that pre-numbered labels for additional sites can be provided.
2. Some health departments may decide to offer testing only during their STD clinic sessions, while others may offer the testing at other specified times or at any time. Each health department should decide how to schedule availability of testing.

C. Who to test

1. Those requesting a test will have different reasons for doing so:
   a. Member of a high-risk group, e.g., homosexual, bisexual, intravenous drug abuser
   b. Recent recipient of a transfusion
   c. Recent positive HTLV-III antibody test, e.g. at a blood bank
   d. "Worried-well," e.g., one gay encounter years ago
2. Those who have recently had a positive antibody test should not be retested. They should be referred to their personal physician for medical evaluation; an additional test will not provide them with any additional information *without* a medical evaluation. Although the Red Cross will not be referring any positives to the health department, some of those individuals may request an additional test at the health depart-

From the Epidemiology Section, Division of Health Services, Department of Human Resources, Box 2091, Raleigh 27602-2091.

ment. Individuals with positive tests should not be retested by the health department for at least six months from the date of their initial positive test.

D. Confidentiality/record keeping/ reports

1. Testing will be anonymous. Even though an individual may be known at the health department, the patient's test results should not be posted to any record with his/ her name.
2. Those tested will be given a card with a code number which will be used on the lab requisition form and specimen. Pre-numbered labels will be provided by the STD Branch. The patient must return with this card to be given test results.
3. A very simple record of those tested will be maintained on a log sheet with numbers corresponding to the pre-numbered labels. The following information should be documented on this log sheet: the date tested, the date results returned from the lab, the test results, and date post-test counseled. If a person was only counseled and not tested, the date of the counseling session should be recorded on the bottom of the log sheet.
4. The only report requested is a copy of the log sheet of those tested. This should be sent to the STD Program Regional Office 15 days after the end of the testing month.

Specimen Collection Protocol

The N. C. State Laboratory of Public Health will accept human sera from patients of Local Health Departments for the detection of antibody to HTLV-III. Specimen collection and transport kits for HTLV-III antibody are available free of charge to Local Health Departments by writing or calling the State Laboratory Mailroom, P.O. Box 28047, Raleigh, N.C. 27611, telephone: (919) 733-7656.

Specimen collection

1. Aseptically collect a blood sample into a 7 mL sterile red top vacuum tube.
2. Allow the blood to clot.
3. Centrifuge the blood at 2000-3500 rpm's for 10 minutes.
4. Transfer the serum into the plastic screw cap vial provided in the specimen transport mailer.
5. Removal of the serum from the clot as soon as possible reduces hemolysis.
6. A minimum of 2 mL of serum is required.

Labeling specimen and DHS form 1424

Five duplicate prenumbered labels are provided for each specimen and corresponding records. The form to use for submitting serum for this test is DHS 1424, Viral Culture and Non-Syphilis Serology. Labels should be affixed as follows:

1. Tube of blood.
2. Plastic serum transport vial.
3. Patient code card.
4. First and second copy of DHS Form 1424 in the area marked "patient name."

Completion of DHS form 1424

1. Write or stamp the return address of the county on both copies of DHS Form 1424.
2. In the area marked "Specific Agent(s) or Disease Suspected" write HTLV-III Antibody.
3. Fill in the collection date, and the age, race and sex of the patient.
4. No other test will be performed on this specimen except the HTLV-III antibody test(s).

Specimen transport

1. Insert the labeled vial of serum into the plastic bag provided.
2. Wrap the completed DHS Form 1424 and the cardboard insert around the bag with vial.
3. Place this into a non-syphilis serology mailer with a blue tape band.
4. Stamp the health department return address on the outside of the mailer and submit to the Laboratory.

If you are notified by the State Laboratory that the specimen was unsatisfactory for any reason, recollect the specimen when the patient returns for the results. Assign a new patient code number. Do not reuse previously assigned number. Technical questions should be addressed to the Virology and Serology Branch, State Laboratory of Public Health, P.O. Box 28047, Raleigh, N.C. 27611. Telephone: 919/733-7544.

Protocol For Pre-Test Counseling

Those individuals inquiring about or requesting the HTLV-III antibody test will have their own particular expectations of what information the test will provide. This test will probably not fulfill all of their expectations. Without a basic understanding of what information this test can or cannot provide, they could easily be misled by the test results. They should be prepared to deal with the ambiguity of the results and the possible social repercussians of this test.

The purpose of pre-test counseling, then, is to provide the individual seeking the antibody test with enough information to make an informed decision. To achieve this, the counselor should review the "Pre-Test Information Sheet" with the patient. Only through interaction with the patient can the counselor feel relatively confident that the patient will make an informed decision whether or not to have this test.

A counselor could easily spend thirty minutes or more in pre-test couseling. In a busy clinic, only five minutes may be available. Since time will be a major problem, the counselor should focus only on the essential points while reviewing the "Pre-Test Information Sheet" with the patient.

Those individuals selected to provide counseling should understand some basic facts about HTLV-III antibody testing:

1. The test is of very limited diagnostic value. It is designed to detect antibodies to the virus thought to cause AIDS. Its intended use is to screen blood to protect the nation's blood supply.
2. A positive test most likely means that an individual has been **exposed** to the virus and produced antibodies. It does **NOT** mean that he has AIDS or will develop AIDS.
3. The individual *could* be infectious, so precautions should be taken not to spread the virus.
4. At present, viral isolation can only be performed in sophisticated research labs.
5. False negatives are possible, especially in high risk individuals (homosexuals and intravenous drug abusers).
6. False positives are more likely to be seen in individuals at low risk. All patients with positive results need to consult their personal physicions for medical evaluation.

Outline for Pre-Test Counseling

1. Reason for exam

Many people may begin by simply asking if they can have a test for AIDS. Ask why they want to have the test. Briefly explain that those in high risk groups (homosexuals/intravenous drug abusers) should already be following prevention recommendations not to donate blood and to engage only in "safe sex," i.e. using a condom. Let them know that this is *NOT* a test for AIDS. Consider following the outline below.

2. Four major points

Using the "Pre-Test Information Sheet," stress the following points:

a. **This is not a test for AIDS.** This is a screening test to protect the nation's blood supply. At this point in time, we do not fully know the implications of a positive or negative test.

b. **A positive test** does not mean one has or will develop AIDS.

c. **A negative test,** especially in high risk individuals, does not necessarily mean one does not have or will not develop AIDS (explain high risk if this has not previously been discussed).

d. **Consequences** — You should be aware that information about a person's positive test results could cause problems with employment, insurance, etc. If they should confide in their coworkers, for instance, word could get out about their test results. The health department will guard confidentially by offering anonymous testing.

2. Decision to be tested

After reviewing these points, ask the patient, "Do you have any questions? If your results are positive, what will this mean to you? Are you still interested in taking this test after hearing all of this?"

3. Information about taking the test

If they decide to take the test, read or discuss the steps taken to preserve confidentiality. Stress the need to return the card to get their results. Patients should understand that the health department can do little more than offer them the test. They will be referred to their personal physician if results are positive.

4. General suggestions

If not previously discussed, explain what groups are at greater risk of contracting AIDS. It is particularly important that high risk group members follow the suggestions provided, whether or not they take the test. Even if results are negative, these suggestions should be followed because of the possibility of a false negative.

Protocol for Post-Test Counseling

No matter how much time was spent in pre-test counseling, test results must be carefully interpreted to the patient. Individuals in high-risk groups with negative results need to be properly counseled. The psychological impact of positive test results should not be underestimated. The patient is not necessarily prepared for positive results simply because he or she requested the test. Try to provide post-test counseling in a nonjudgmental manner. The counselor should be understanding and supportive. The following guidelines are suggested for post-test counseling.

Negative results

1. After informing patient of his negative results, discuss the possibility of a false negative. High-risk individuals could possibly be infected and able to spread the virus.
2. High-risk individuals with negative results need to be reminded not to donate blood and to continue safe sex practices (no exchange of body fluids/use a condom).

Positive results

1. Provide Information
   Review the points on the POST-TEST information sheet with the patient. Be ready to respond to any questions the patient may have.
   a. *This is NOT a test for AIDS.*
   b. *A positive test does NOT mean you have or will develop AIDS.*
   c. *Social relationships with family members may continue.*
   d. *Consult your physician/follow prevention precautions.*
      (1) Until properly evaluated, the individual should be considered infectious.
      (2) Discuss prevention — briefly review the list of precautions, respond to questions.
2. Referral
   a. Advise the patient to consult his/her personal physician for further medical evaluation. To

inform their physician, write "POSITIVE ELISA FOR HTLV-III ANTIBODIES" on the cord with their code number. The patient should be requested to give this card to his/her physician.

b. If the patient does not have a personal physician or needs further information or would like referral to a support group, have them call the toll-free Hotline in Raleigh, 1-800-225-AIDS. This Hotline will be staffed from 8 am to 5 pm Monday through Friday beginning May 1, 1985.

c. If the patient is extremely emotional and you are concerned about their reaction to the information, consider contacting a community mental health center.

Pre-Test Information Sheet for the HTLV-III Antibody Test

If you want an HTLV-III antibody test, consider the following before making a decision:

1. This is NOT a test for AIDS. This test screens blood for antibodies to the virus (HTLV-III) thought to cause AIDS, thus helping to protect the nation's blood supply. Antibodies are what the body produces to fight infections.
2. A POSITIVE test does NOT mean a person has or will develop AIDS. Some tests will be falsely positive. For others, a positive test may mean one has been exposed to HTLV-III, and the virus may be present (this is especially true for high-risk group members). Based on what is known now, only a small number of people infected with the virus will develop AIDS.
3. A NEGATIVE test (especially for high risk groups members) does NOT mean an individual does not have or will not develop AIDS. It is possible to be infected with the virus and have a negative test.
4. Information about a person's positive test results could cause problems with insurance, employment, etc. Although health departments will offer anonymous testing, people should still be aware of these possible problems before taking this test.

Please consider this information carefully before you make the decision to have this test done.

For those who choose to have the test

Your name will not be used on any record or lab slip for this test. You will be given a card with a code number. To get your test results, bring this card to the health department seven days or later from the date you took the test. You will NOT be given your results unless you have your card. These steps are necessary to protect your privacy.

Positive test results

If your results are positive, you will be advised to seek medical evaluation from your personal physician. The health department is unable to provide this type of care.

High risk groups

Those in high risk groups are more likely to have been exposed to the virus causing AIDS. The following are thought to be high-risk:

1. Anyone with signs or symptoms of AIDS.
2. Males who have had sex with more than one male since 1979, and males whose sexual partner has had sex with more than one male since 1979.
3. Past or present abusers of injected drugs.
4. Hemophiliacs.
5. Sexual partners of persons in these groups.

General suggestions

Persons in high risk groups should NOT donate blood or blood products *regardless of their test results*. To reduce the chances of acquiring or spreading infection, limit the number of sex partners and use a condom.

Information for those with a Positive HTLV-III Antibody Test

1. **This is not a test for AIDS!**

   If your test is positive, it means you may have been exposed to the virus and have developed antibodies (the body's defense against the virus).

2. **A positive test does *not* mean that you have or will develop AIDS.**

   As with any other tests, there are people who are falsely positive. Some people may have a positive test who have never been exposed to the virus.

   For others (especially high-risk group members), a positive test may mean one has been exposed to the virus. Even this does not mean you will develop AIDS. Based on what is known so far, only a small number of people infected with the virus will develop AIDS. In fact, many infected people may not develop any illness at all. There is no information at the present time to predict which persons with the antibodies are more likely to develop AIDS-related conditions or AIDS itself.

3. **What does a positive test mean for family members?**

   There is no evidence to suggest that HTLV-III is spread by casual contact. Social relationships with family members and friends may continue.

4. **Consult your physician for further evaluation.**

   If you have been exposed to the virus, you may be able to infect others. Until you have been checked by your physician, follow these steps:

   a. Do not donate blood or plasma, sperm, body organs, or other tissues.

   b. Avoid spreading the virus to

others thraugh sexual intercourse and avoid expasure to saliva through aral-genital contact or intimate kissing. If you decide to continue sexual activities, use condoms.

c. Tell your sex partner(s) about your test result and encaurage them ta see a physician.
d. Avaid sharing personal items, such as razars and toothbrushes.
e. If you cut yourself and spill blood, wash the area where the blood has spilled with a water/bleach mixture (ane part bleach to ten parts water).
f. Tell your physician and dentist about your positive test.
g. If you are a woman with a positive test, you should avoid pregnancy until you have been checked by your physician.
h. If you inject drugs, do not let others use needles you have used and do not use someone else's needles.

N.B. The information in this article is taken from instructians by the North Carolina Division of Health Services distributed to local health departments on establishing alternate test sites for HTLV-III antibody. It is provided for your information since it is entirely passible that you may have a patient referred to you with a positive test for this antibody. Because of limited funding and the fact that this test is available in commercial labs, the North Carolina Division of Health Services Lab will **not** be able to provide HTLV-III antibody testing for anyone except local health departments.

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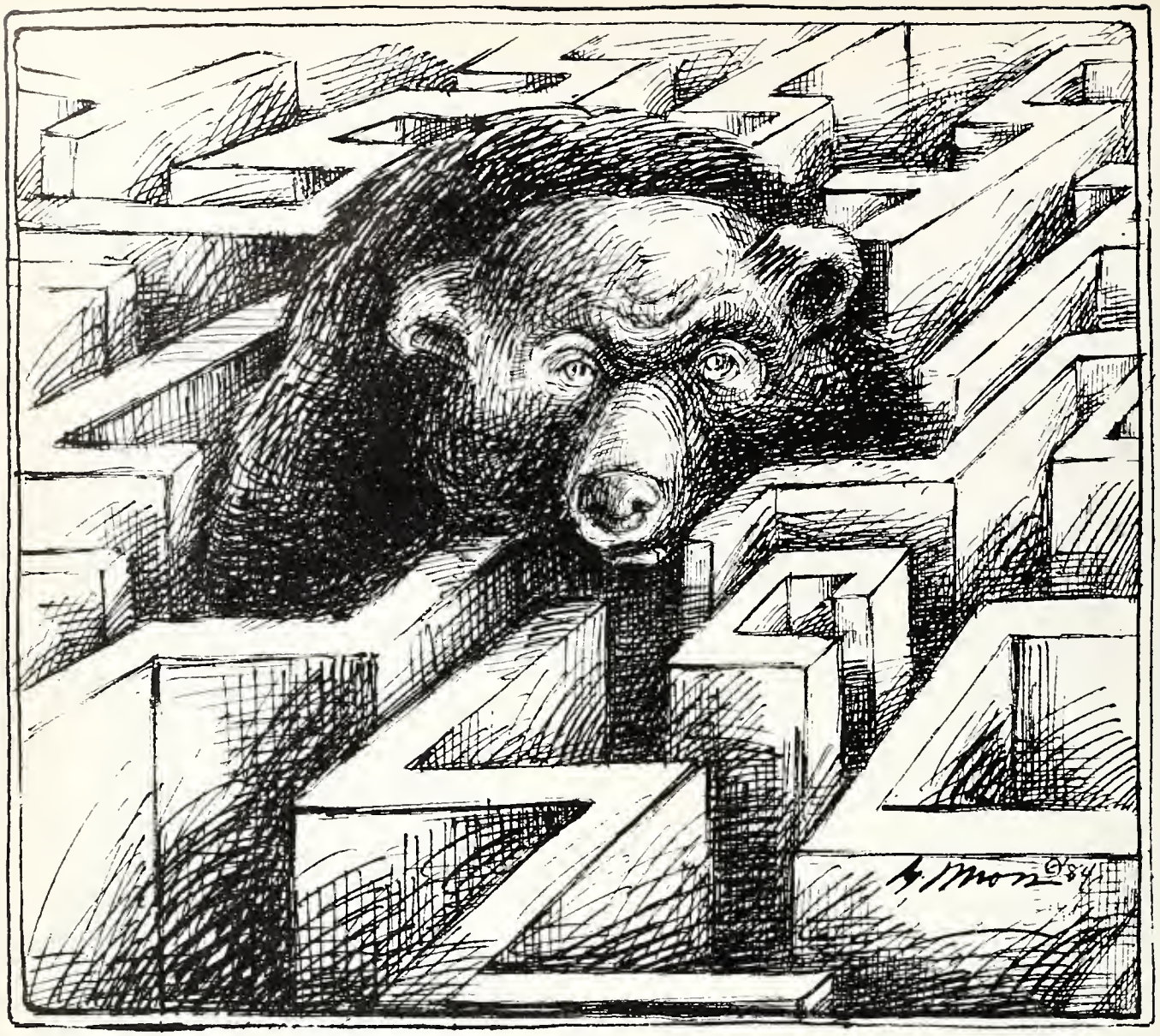
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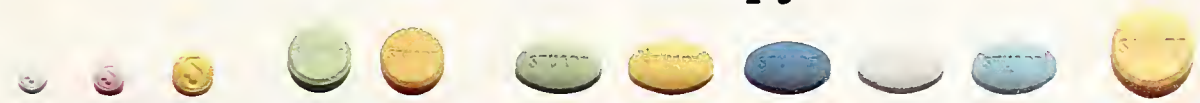


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WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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Old Tobacco

John Henry McWhorter, M.D.

• *Tobacco has been a part of life in the Carolinas for a very long time.*

THROUGHOUT the millennia, man has repeatedly smoked various substances. Yet is is to the New World Indians that we owe the origin and smoking of tobacco.[1]

Originating from a word for a West Indian tube with which snuff was drawn into the nose, tobacco is a genus *(Nicotiana)* of the nightshade family *(Solanaceae)*. Only two of the more than fifty species have enjoyed historical importance — *N. tabacum,* indigenous to South America, and *N. rustica* of the West Indies and North America east and immediately west of the Mississippi River.[2]

The colonists of 1586 returned from Virginia to England and planted *N. rustica* on their return.[2] The early European explorers seized upon tobacco as the panacea for their ills,[2] and addicted sailors spread the seeds to their ports of call.[3]

John Rolfe introduced the more aromatic *N. tabacum* in 1611 from the Spanish American plantations. The business success of the species soon established its dominance. A raging controversy over health hazards has raged since tobacco's introduction into European life.

The figure shows several plants of *N. rustica*. Its history among the native North Americans is an interesting one, not only from its patterns of use, but from its continued cultivation and use today, especially in the Carolinas. The myths surrounding its origin among the Cherokee offer a rich cultural lore. Its use was ritual and medicinal, rather than habitual. To the Cherokee, *N. rustica* was the original tobacco and was known to them as *tsâl-agăyûñ'li* or "old tobacco." It was used as an incense or guarantor of an oath, and was smoked either communally or individually in a pipe, or sprinkled on a fire.[4]

The principal historical record of "old tobacco" among the Cherokee comes from the work of James Mooney and Frans Olbrechts, who translated Cherokee manuscripts, the most noted being that of Swimmer, a prominent medicine man of the time. They describe the use of dry, crushed *N. rustica* in a fire at a patient's house to keep witches away. Due to its scarcity, it was often mixed with ordinary smoking tobacco,[5] which is still done at present.

It was one of a few medicinal plants cultivated for use, as opposed to the custom of going up the mountains to collect them,[5] a practice still followed at the present time.

From Box 201, McWhorter, WV 26401.



Nicotiana Rustica

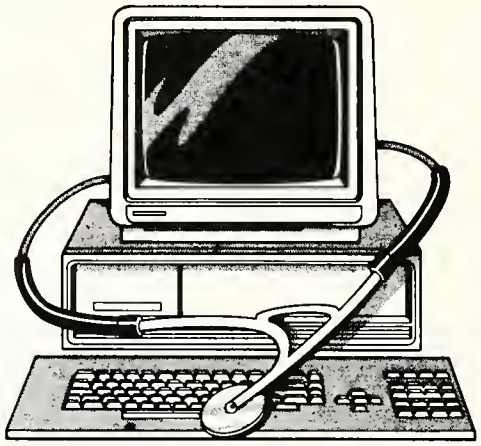
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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

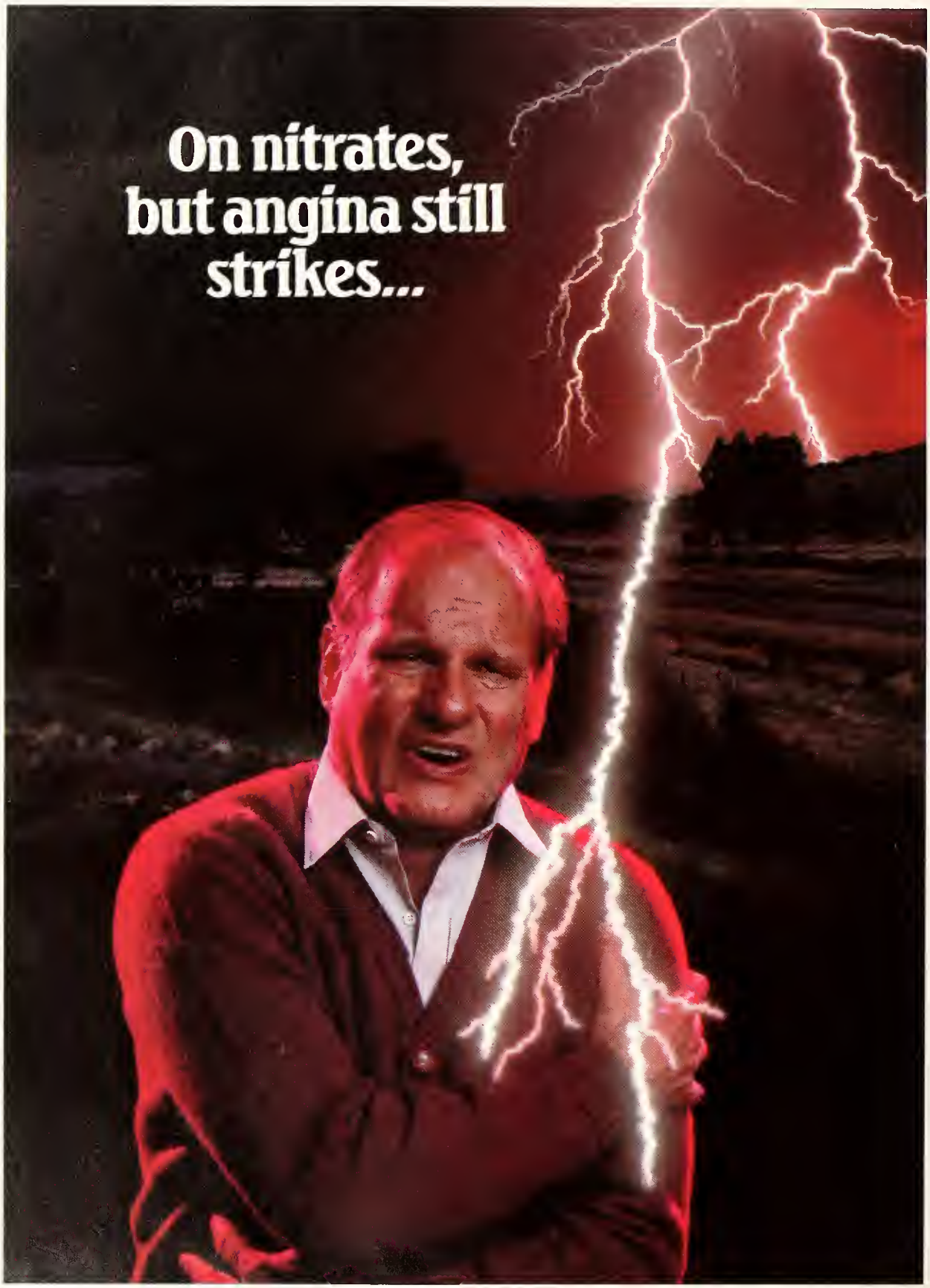
Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

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ISOPTIN. Added antianginal protection without beta-blocker side effects.

Please see brief summary on following page.

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See *Precautions.*) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under *Precautions.*) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block 3rd degree (0.8%), bradycardia HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings*.) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984. 2385

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Medical Student Research in the 1940s

John B. Graham, M.D.

• *This is Dr. Graham's address at the first convocation of the John B. Graham Research Society at UNC in January 1985.*

I was very impressed today by the quality of the research which you, our medical students, have been doing. I listened to 14 excellent papers. The contrast between these and what my contemporaries and I were doing at a similar stage of development is very stark. What I observed was the application of state-of-the-art concepts and procedures, and the positing of hypotheses which were gauged to obtain answers to serious questions. I thought it might be amusing for you to hear how different things were when I was a student 45 years ago.

I entered medical school in Chapel Hill from Davidson in the fall of 1938, completely unaware of the possibility that a medical student might be involved in research. Even if I had known, I probably would not have become so engaged. Like most of my peers, I was anxious to obtain my medical degree before we entered World War II, which was already getting underway in Europe. I would have regarded research as a potential diversion which might produce academic failure which would make me eligible for the draft, and the possibility of becoming a foot soldier. The irony is that the battalion surgeons of the US infantry in World War II, who were the most forward-placed of all doctors, were drawn largely from the medical school classes of 1941 and 1942 (my own). Despite my complete lack of clinical training and after having spent 2½ years in Pathology, I became the surgeon of the 2nd Battalion of the 307th Infantry, 77th Infantry Division and served in the battle of Okinawa.

The medical school in Chapel Hill consisted in 1938 of a two-year basic science curriculum, managed by about 20 bona fide faculty members for 60 students. Perhaps five of the faculty were doing publishable research. Research grants were unknown, except for a few Rockefeller and Markle Foundation grants, but the NIH as we know it today is a postwar phenomenon. One of the active researchers was the late Russell Holman of Pathology. He was helped in his experiments by a series of student research assistants of whom Dr. Margaret Swanton, formerly of our department and now practicing in Clinton, was one. Another was Dr. Gilmer Mebane who still practices in Rutherfordton. Arnold Breckenridge, who lost his life in service during World War II and is memorialized by the Spicer-Breckenridge Lectureship, performed a similar function for Dr. MacNider. These students were working their way through a two-year curriculum over a three-year period as research assistants. My guess is that they received little compensation other than remission of tuition.

At Cornell, where I did my clinical years, a few of my classmates also did research as students. Three of them — Charles Breedis, Carleton Hunt, and Walter Riker — went on to become prominent scientists, but most of my contemporaries at Cornell were driven by the same imperatives as those at Chapel Hill and were headed for war and practice. I had very little contact with the faculty at Cornell until my final semester which began immediately after Pearl Harbor. Two of the three Pathology residents were being drafted, and I was asked to start my internship six months early to help fill the manpower gap. This meant that I would be given room, board, uniforms and laundry in exchange for doing autopsies at night and on the weekends. I was also expected to operate the Blood Bank on alternate nights. The "take home pay" was $25 a month, provided by the Blood Bank. My mother and I welcomed this financial assistance, but I essentially dropped out of medical school. I never attended clinics in the surgical specialties, and to this day I am completely ignorant of Ophthalmology, Urology, ENT, and Orthopedics (I hope it doesn't show!). I spent 2½ years as a house officer in Pathology at the New York Hospital, however, and it was during this period that my research career began. I can only characterize these activities as "what happens when you are just standing around." I think you will see what I mean.

My first publication[1] grew out of an autopsy and concerns a disease of the kidney which was then so obscure that there was not a description of it in the English language. My involvement came about this way. (Ruby, my then recently-acquired wife, remembers it well.)

Pathology residents at New York Hospital in those days did all the autopsies performed at night and on weekends. The senior staff did the daytime cases, Monday-Friday. This policy was based on the premise that an autopsy was an important teaching exercise and that the most, not the least, experienced persons should do them if possible. (WW II changed many things in addition to the face of Europe. I doubt that many living physicians have ever seen a Professor do an autopsy.) The time was the fall of 1943, I think, when I was for a short period the only house officer in Pathology. At about 8 o'clock on a Sunday morning, the telephone rang. "Autopsy, Dr. Graham, and the clinician wants it done right away." I griped and my wife grumbled, but I got dressed and went to the morgue. The deceased was a small girl. Her main clinical problem appeared to have been severe anemia which had required transfusions, but she had also been uremic. I found her kidneys to be small

From the Department of Pathology, UNC, Chapel Hill 27514.

and fibrotic and to contain many small cysts. These were unusual in being located in the medullary regions rather than the cortices. I completed the autopsy as rapidly as I could and returned home to read the *New York Times*.

It later transpired that a similar case had been observed in Germany in the 1920s, but this single report was essentially unknown except to the readers of Henke-Lubarsch's *Encyclopedia of Pathology*, an 18 volume set printed in German. Fortunately, we had access to Henke-Lubarsch, because Dr. William Dock, the Professor, was fluent in German. He uncovered the previous case for us. We designated the syndrome "Medullary Cysts of the Kidney with Anemia," anemia being included in the title because the clinician was Dr. Carl Smith, the hospital's pediatric hematologist, the person to whom the child had been referred.

I consulted Carl Gottschalk's two-volume text on kidney disease yesterday (it is mysteriously entitled *Strauss and Welt's Diseases of the Kidney*, 3rd edition) to see whether he had gotten the story straight. I was pleased at how his account begins: "In 1945, Smith and Graham reported the case of an eight year old white girl who presented with severe anemia of 1 year's duration, who was suffering from renal failure, and whose kidneys at death were found to have medullary but not cortical cysts. In the 3 decades since then over 250 cases . . . have appeared in the literature, etc." The point of this story is that I became an author solely because a child had died on the weekend when no one else was available to do the autopsy. If she had survived until Monday, one of the senior staff would have done the case and become the co-author. This event emphasizes the importance of careful scientific planning.

My next publication is one which I have never discussed publicly. In fact, I did not list it in my CV for 25 years fearing that, if my association with it were known, it might jeopardize my career. Now that I am retiring, I shall come out of the closet, and tell all.

When I left New York Hospital in July 1944, I joined the Army and spent 18 months overseas in the Pacific Islands and Japan. I returned to Chapel Hill in September 1946, and sometime during the next year received a letter requesting a reprint of a paper in the *Journal of Investigative Dermatology*. I thought there must be some mistake and visited the library. I discovered to my astonishment that I was an unbeknownst author. The title of the paper which I had co-authored was "Absence of Thrombo-angiitis Obliterans in Experimental Dermatophytosis."[2] The text explained that the authors had produced chronic infections of the footpads of 8 castrated (?) rabbits, had maintained the infections for 18 months, and had then demonstrated that obliterative arterial lesions were not present in their lower extremities. The patency of the arteries had been demonstrated by injecting them through the aorta with radio-opaque material and X-raying the legs. (This is the same procedure which Dr. Fred Dalldorf still uses at NC Memorial to examine the coronary arteries in patients who have died of heart disease.)

Suddenly the penny dropped. I remembered what had happened. I had been having lunch in the doctors' dining room at the New York Hospital with an affable dermatologist who had been repatriated from Shanghai on the Gripsholm several years earlier. He was trying to figure out how to examine the arteries of some rabbits which might have developed obliterative arteritis in their lower legs. I casually suggested that he might inject the arteries with a radio-opaque mass and X-ray the legs. The next morning when I came to work, I found a dead rabbit in front of my office door wrapped in a newspaper. I took the rabbit to the morgue out of curiosity, injected the aorta, X-rayed the legs, and obtained a nice arterial pattern. The following day I found another dead rabbit in front of my door. This pattern was repeated for, I suppose, a week since the paper mentioned eight rabbits. But I was very busy at the time and really didn't want to become involved with such a "mickey-mouse" project. I was now the Resident and had only one helper, a dumb intern from California named Sam. He and I were having to do *all* the autopsies, because the draft had finally caught up with the faculty. I tried to get Sam interested in the research project, but he wasn't as dumb as I had thought. So I placed the dead rabbits out of sight in a refrigerator to wait until I could get to them. My last act at the New York Hospital before departing for Carlisle Barracks in July was to inject the refrigerated rabbits, X-ray their legs, and send the films to the dermatologist. I had completely repressed the memory of those silly rabbits, and had I not received a reprint request, I should never have known that I am an authority on the non-relationship between athlete's foot and Buerger's disease. I don't know what the moral of the story is, except it certainly was easy to become a research collaborator in the old days!

My final story concerns Dr. Saxton's rats. He was studying cancer in rats using Harry Green's technique of implanting a bit of tissue in the anterior chamber of the eye and observing it directly. The rule-of-thumb was that benign tissue regresses and malignant tissue extends. He was interested in chromophobe adenomas of the rat pituitary, and had transplanted small bits into the eyes of about 50 rats. (The next step in his protocol was to sit back to see what happened, and the experimental period was up to two years of observation!)

In the middle of his experiment Dr. Saxton got an offer to move to Washington University in St. Louis, his home town. He asked me to continue measuring the size of the tumors at monthly intervals, then remove the tissue for sectioning at the end of the experiment. I followed his instructions, more or less, and he was kind enough to place my name on his paper.[3] Just before leaving New York, I received a letter from a well known cancer researcher asking a technical question about the experiment. He wished to know why we had anesthesized our rats with chloroform rather than ether when implanting the tumors. I didn't have a clue. In fact I had never seen Dr. Saxton operate. I called him in St. Louis and, after reprimanding me for making an unnecessary call during wartime, he explained. "It is very obvious. I like to smoke when I operate, and chloroform is not explosive like ether."

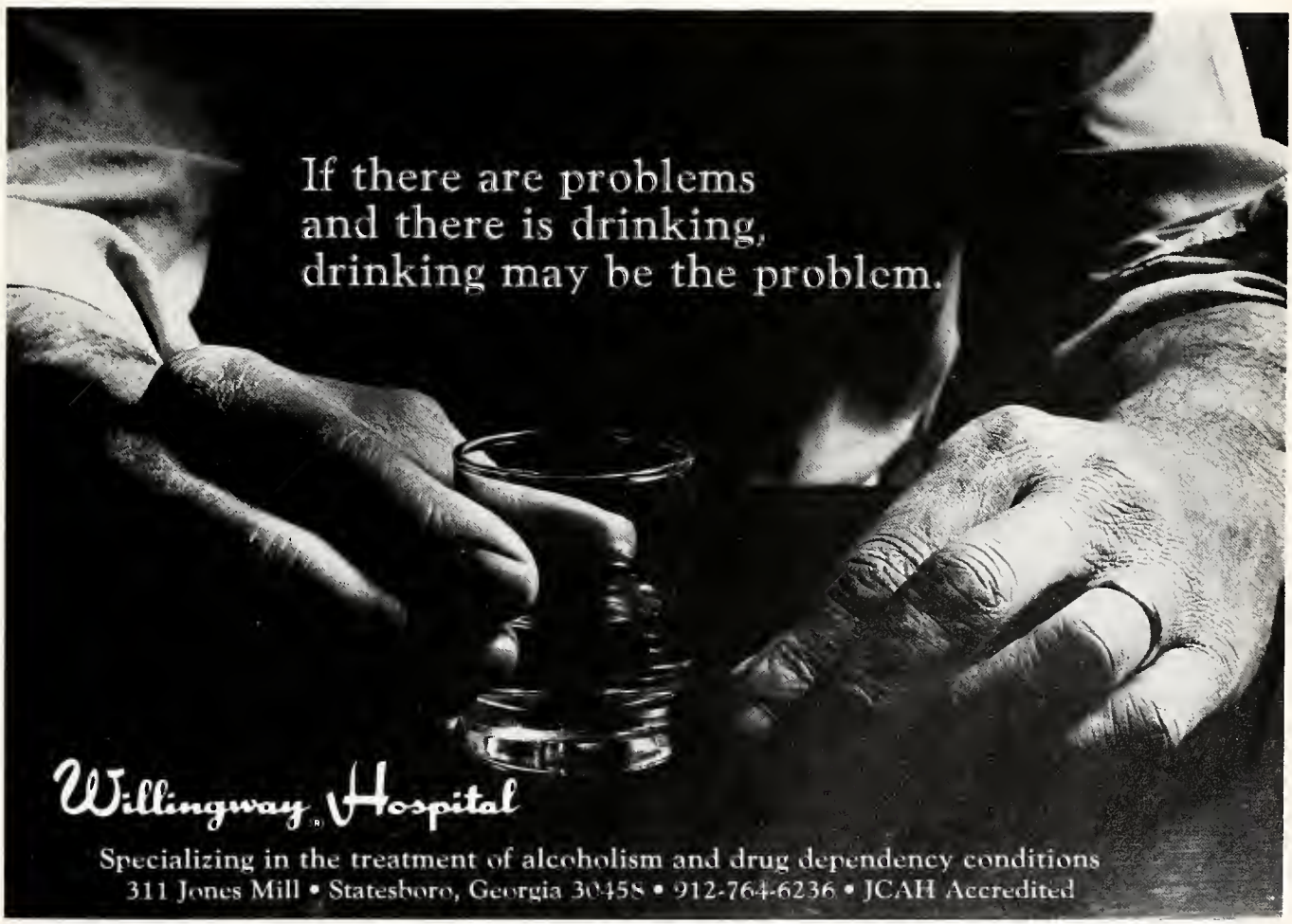
I think I learned an important lesson from Dr. Saxton's rats. I have been very skeptical ever since about the significance of the very detailed descriptions of "Methods and Materials" which one finds in certain journals (e.g., *JBC*, *JCI*). I have found it to be faster, cheaper and more rewarding to visit the lab of someone who has developed a new technique than to try to establish the procedure from what

has been printed. Very often something crucial has been omitted and the omission not recognized because of the verbiage. These tedious descriptions are more valuable sociologically than scientifically.

But the phrase "smoking while operating" has a very contemporary ring. It reminds me of a recent story in my favorite newspaper. You may recall that at the Baby Doc School of Medicine in Port-au-Prince, Haiti while Dr. Janata was transplanting the liberal heart of a Volvo-driving Yuppie into the conservative body of a banker, President Raoul Duke stood by the operating table unmasked, with a can of beer in his hand and a cigarette holder in his mouth. Could it be that Raoul Duke is one of Dr. Saxton's descendents?

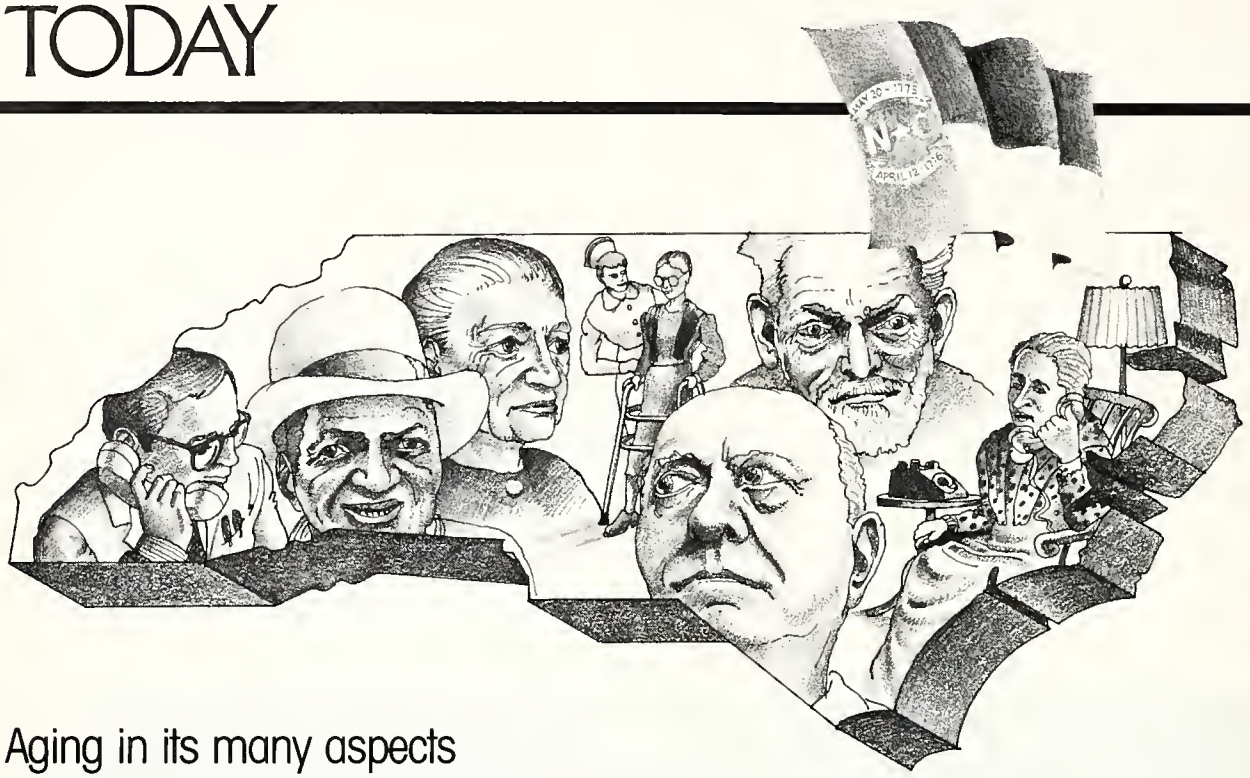
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NORTH CAROLINA MEDICINE TODAY



Aging in its many aspects

It is estimated that 25 million people (11% of the population) are over age 65, and represent the fastest-growing segment of the population by far. It is further estimated that this group currently spends approximately 75 billion dollars annually for personal health care, and accounts for some 55% of all federal health dollars.[1] For these reasons alone, studies concerned with various aspects of aging are of vital importance to the entire nation. Much major research in this complex area is being conducted in North Carolina, at its several medical centers and universities, often under grants from the National Institute on Aging.

Studies cover a wide range

Recent studies have reported on the physiological dynamics of aging as related to circulatory diseases and circulatory risk factors at advanced ages (over 85) as compared to findings in a study population with a mean age of over 70 years.[2] Another study, stemming from the comprehensive Duke First Longitudinal Study, evaluated Wechsler Memory Scale scores as related to distance from death and the potential use of the WMS as a predictor of survival in both normal and demented elderly populations,[3] while yet another compared young and old adults in the spontaneous use of context to learn and recall information.[4]

Dealing with America's fourth leading killer disease

Researchers at Duke University Center for the Study of Aging are focusing on the study of Alzheimer's disease, a type of primary neuronal degeneration that is the most common form of dementia. Estimates vary but indicate that as many as 4 million older Americans[1] are afflicted with this illness, which has been labeled "the disease of the century."[5] Concurrent with its medical research on Alzheimer's disease, the Duke University Center is providing innovative support mechanisms for afflicted families and other caretakers. A hotline provides callers with telephone consultations, introductions to others close by in similar circumstances, and practical medical, legal and psychological information. The Center has also aided in the establishment of 19 local support groups statewide, and regularly makes available information on Alzheimer's disease to health providers, nursing homes and hospitals, and others responsible for programs and services directed toward the victims of this killer disease.[6]

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*Feighner JP, *et al. Psychopharmacology 61*:217-225, Mar 22, 1979.

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Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and blooting. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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EDITORIAL

In Support of a Model Bill Allowing the Use of Insect Sting Kits by Trained Laymen

Claude A. Frazier, M.D.

I have good news and bad news. The bad news is that any one of you could be stung and die within five minutes; you would not have to have had a previous reaction to an insect sting. The good news is that someone might be present who had a pre-packaged epinephrine syringe and was trained to give an injection. He could buy time to get you to a physician or hospital.

Some years ago, after treating a number of patients who suffered near fatal anaphylactic shock reactions to insect venom, I determined to make this branch of allergy a focus of my concern, and I gathered as much information as I could on the subject. This appeared in 1969 as a textbook, *Insect Allergy — Allergic and Toxic Reactions to Insects and Other Arthropods*, published by Warren H. Green, Inc. in St. Louis. A revised edition will be published soon.

Over the years I have discovered a good deal of ignorance not only among the general public but also among physicians as to both symptoms and proper treatment of an anaphylactic reaction to an insect sting. A number of fatal reactions have been misdiagnosed as "heart attack" or "death from natural causes," so the problem is greater than statistics presently indicate. I believe most of these deaths were unnecessary.

Anaphylactic shock reactions to food or drugs are perhaps more likely to be correctly diagnosed simply because no other cause seems reasonable at the moment. Someone who has just eaten shellfish, for instance, and then almost immediately exhibits systemic symptoms is more likely to recognize the cause as "something he ate." Allergy to insect venom is often surrounded by misunderstanding and misinformation.

After suffering an anaphylactic shock reaction to an insect sting, some patients have been told by their physicians to simply take benadryl the next time they are stung. In my hometown, a physician gave benadryl to a young man who had a history of reaction to an insect sting. This man was in the woods fishing, in an isolated area, and was stung. He died. His mother, having been told by one of my patients about the insect sting kit, called me three different times to ask if her son's death could have been prevented. To keep the doctor from being sued and to relieve her guilt, I told her that nothing was 100%. That same doctor was seated next to me at a medical meeting later and he had seen another patient similar to the one who had died. "What did you give him to carry?" I asked. His answer, "Benadryl."

Benadryl will not stave off a severe systemic reaction. On the other hand, only a small dose (0.3 to 0.5 cc) of injectable epinephrine can give pause to rapidly intensifying and potentially fatal anaphylaxis long enough to transport the patient to a physician or hospital.

I can cite a number of cases of both fatal reactions and misdiagnoses. For example, an obituary in a local paper states that a 57-year-old man was stung in the arm while fixing his car; he was dead on arrival at a hospital less than an hour later. No one, evidently, was aware that he was allergic to bee venom.

For example, a well-known newspaper man was out jogging and his death was attributed to acute heart failure. Even though just before he collapsed he was heard to say that he had been stung and the autopsy findings were consistent with fatal anaphylactic shock, his death was misdiagnosed.

A man died unexpectedly while on a fishing trip in Transylvania County. He had suffered a bee sting before death occurred.

A pediatrician called me to say that three of his young patients were allergic to insect stings but that the school nurses could not give them a dosage of epinephrine if they were to be stung. He said, "Would you call this stupid Superintendent of Education and tell him to make them treat these patients if they are stung?" I explained to him that it was not a stupid superintendent but a stupid State law. I suggested the "Good Samaritan law" but he said, "These school nurses and teachers will not do anything until it is a written law of this State. They are afraid."

Fatal outcomes can be prevented. Death due to venom from one or two insects, from the ingestion of a food or the injection of a drug is essentially needless. Programs to train people who are in positions of responsibility for public safety to recognize systemic symptoms of allergy and to administer pre-measured injectable epinephrine subcutaneously when a physician is unavailable can save lives that might otherwise be lost.

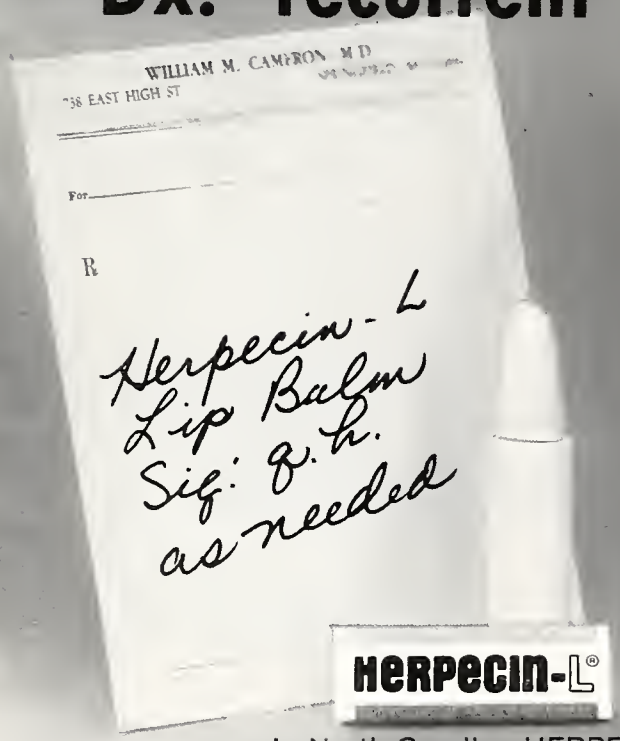
Such a program has received the support of the American College of Allergists, the American Academy of Allergy, the American Academy of Pediatrics and the American Academy of Family Practice. It has also been commended by a number of physicians as a step toward emergency first-aid care for the public.

From Bldg. 4, Doctors Park, Asheville 28801.

The most recent development has been for the American Medical Association to revise the previous version of the model bill. I have worked with the legislative branch of the AMA for years trying to work out a model bill. At one point I thought they might withhold their support by rescinding the model bill. At that point I had to speak before the legislative branch and try to convince them otherwise. Since that time support has been stronger than ever. The revised edition of the model bill will discourage lawsuits being brought against the trained layman who administers epinephrine as a "good samaritan."

Only in the 10 states that have passed laws allowing trained laymen to administer the pre-measured epinephrine can a layman legally give this treatment to a person who is suffering an anaphylactic shock. Georgia may become number 11. North Carolina passed its bill on June 11, 1981.

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Brief Summary of Prescribing Information
NORLESTRIN® (norethindrone acetate and ethinyl estradiol tablets, USP)

See section under **Special Notes on Administration and HOW SUPPLIED.**
Before prescribing, please see full prescribing information. A Brief Summary follows.

DESCRIPTION
Norlestrin Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE
Norlestrin Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 woman-years; in clinical trials with Norlestrin 2.5/50 involving 96,388 cycles, there was a pregnancy rate of 0.22 per 100 woman-years.

Dose-Related Risk of Thromboembolism from Oral Contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders.
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral vascular or coronary artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed abnormal genital bleeding.
7. Known or suspected pregnancy. (See WARNING No. 5)
8. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular Disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial Infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of Dose: In an analysis of data, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptives, however, the quantity of estrogen may not be the sole factor involved.

Persistence of Risk: Two studies have suggested that an increased risk may persist for as long as 6 years after discontinuation of oral contraceptive use for cerebrovascular disease and 9 years for myocardial infarction. In addition, a prospective study suggested the persistence of risk for subarachnoid hemorrhage.

Estimate of Excess Mortality from Circulatory Diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions.* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

3. *Carcinoma.* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors.* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy. Birth Defects in Offspring, and Malignancy in Female Offspring.* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possible other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease.* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects.* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache.* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-Feeding.* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected: (a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, tetracycline, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension; gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives; although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted: premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

Special Notes on Administration
Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence, reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Norlestrin [21] 1/50 is available in compacts each containing 21 tablets. Each tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [21] 2.5/50 is available in compacts each containing 21 tablets. Each tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

Norlestrin [Fe] 1/50 is available in compacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [FE] 2.5/50 is available in compacts each containing 21 pink tablets and 7 brown tablets. Each pink tablet contains 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate, USP. Available in packages of five compacts and packages of five refills.

Norlestrin [28] 1/50 is available in compacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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Ecology and Pollution

Eugene W. Linfors, M.D., editor

The question for June is: **What would you advise the North Carolina Medical Society to do and say publicly about ecology and pollution?**

From Dr. Robert M. Hall, Director of Wake County's Department of Health.

What the North Carolina Medical Society, as well as its individual members, can do and say publicly on ecology and pollution was stated very clearly by the participants in an Environmental Health Seminar held in October, 1984 at which the Society was represented. As reported to the Society's President it was the unanimous opinion of the participants that,

> The greatest and most immediate environmental threat that now faces us all is the pollution of our water supplies. Our greatest and most urgent environmental need is for individuals and organizations who are interested in the public's health to become involved in land use planning and land development in suburban and rural areas in order to prevent this pollution of our water.

Urgent as this environmental need was said to be, it is made even more so by the moves now underway in North Carolina to eliminate local boards of health and even to eliminate local health departments and disperse their functions among other elements of county government.

The Environmental Health Seminar was held in Atlanta and was sponsored by the American Medical Association. Its purpose was to focus attention on major environmental and occupational health problems and to encourage cooperative efforts to respond to these problems within the eight southeastern states.

The participants included representatives from the various state medical societies, occupational medical associations, health departments, environmental protection agencies and schools of public health in the eight states, and the United States Centers for Disease Control and the United States Environmental Protection Agency.

The seminar participants were requested to identify the environmental and occupational health problems and needs that confront the populations of these states and recommend appropriate solutions. This they did, identifying specific problems that we face now, as well as others that are potential in nature. As stated earlier, they agreed that the greatest current, specific environmental problem is the threat of pollution of our water supplies as the result of unplanned and uncontrolled land development.

The participants also identified problems or needs of a general nature that must be satisfied if the specific environmental health problems are to be solved.

Communications. The lack of and the resulting need for adequate communications between agencies, organizations and individuals with similar interests, goals and responsibilities in the fields of environmental and occupational health was stressed more often than was any other problem. It was a theme that ran throughout the seminar.

This lack of the necessary communications exists not only between the states, and between them and federal agencies, but within the states themselves. Within the states there are gaps in communications between the various state agencies, between public and private agencies and organizations, and between them and individual, practicing physicians and organized medical entities.

Coordination of Efforts. The lack of and the need for the coordination of the efforts of the various organizations, agencies and individuals with similar interests, goals and responsibilities in the fields of environmental and occupational health was mentioned next most often, as was the obvious fact that the coordination of efforts is dependent upon the necessary communications.

Influence of the Practicing Physician and of Organized Medicine. The importance of and the key role played by the individual, practicing physician and by medical societies was emphasized repeatedly. This was not done by the physicians present, who were in the minority, but by the non-physician participants. At least some of the physicians present were surprised at the importance and influence attributed to them and their efforts by the other participants and found this a somewhat sobering experience.

The participants stressed that both the individual, practicing physician and organized medicine play a key role with respect to the identification of environmental and occupational health problems, the advocacy of the measures that are necessary for their solution and the necessary education of patients, the community and elected representatives.

Education. Physicians are the best possible educators with respect to environmental and occupational health problems and hazards. The need for the education of patients, community groups and legislators was stressed, as was the need for objectivity. Facts must be used; if opinions are stated, they should be identified as such.

Advocacy. Physicians can marshall support and lobby for the definition of public health problems and the measures required for their solution. The Mississippi State Medical Association has opposed, officially and actively, all attempts to establish a high level nuclear waste repository in Mississippi prior to the availability of data assuring

the safety of such a program. At the Seminar its representative urged the "Medical Associations of our sister states to carefully examine the hazards associated with the transportation of high level nuclear wastes through their cities and for the American Medical Association to take a more active leadership role in advising our fellow physicians and the public at large of the health risks of nuclear wastes."

Protagonists on Behalf of the Public's Health. The governmental agencies are unable to lobby on behalf of environmental and occupational health programs. It is essential that non-governmental organizations, such as medical societies, carry out the necessary educational and lobbying measures.

In addition to identifying current and potential environmental health problems and needs, the participants also identified barriers to the prevention of pollution, such as cost, lack of sufficient information, etc. They agreed that the biggest barrier, however, is "politics" and the influence that sometimes is exerted by industry.

This stated need for the protection of our water supplies lends even greater urgency to the need to retain the local boards of health and health departments which protect our people from pollution of their water supplies, as well as from other environmental hazards.

The physicians of the state should know that now, when North Carolina's people face greater environmental health problems than ever before, a move is underway in the state that will eliminate local boards of health and have their functions and responsibilities taken over by county commissioners. Another move is underway that would allow the elimination of local health departments and the assignment of their functions to other agencies of county government. Among those functions are those of the sanitarians who protect not only our water supplies but our milk and other foods and who carry out our epidemiological investigations.

Still other moves have been designed to eliminate the qualified health department directors who supervise and direct these environmental protection activities, among others.

Wake County, as has others, has attempted to prevent the hiring of qualified physicians with public health training and experience as health directors and has attempted to replace these with lay "administrators."

Since public health problems would not even be thought of, much less planned and prepared for, if qualified professionals are not available, one can only surmise why this would be done. One possible reason may be represented by the complete support that has been given the Wake County Board of Health and Health Department by the Wake County Medical Society and its Public Health Committee as the result of the interrelationship between the Committee, the Society and the physician health director.

Another reason may be represented by this article and the influence of those to whom it is addressed.

These moves are made possible by a North Carolina law, N.C.G.S. 153A-77, which authorizes the board of county commissioners in a county that has a population in excess of 325,000 to assume direct control of the activities performed by the county boards of health, mental health, social services and any other boards appointed by them.

Left unanswered is the question of why such a county, with greater and more complex problems as the result of an increasing population would not need these various boards more than ever. An even more pressing question is why this would be done when it is manifestly impossible for the county commissioners to carry out the additional responsibilities of these various boards.

Only one county, Mecklenburg, had a population of this size when the law was passed, in 1974. The Mecklenburg County Board of Health was then eliminated, after which the county commissioners assumed its functions. The health department was then fragmented and a separate department of environmental health was established. The county now has eliminated the boards of mental health and social services and is in the process of placing the remainder of the county health department under an assistant county manager.

Wake and other counties have attempted to do the same thing by having the law amended so that it would apply to counties with populations of less than 325,000.

The current law, while it allows the elimination of the board of health, prevents the elimination of the health department.

Legislation now being proposed for submission in the current session of the North Carolina General Assembly would make this possible.* If it is enacted the commissioners of a county will be able, after abolishing the board of health, to abolish the health department and transfer its functions, including those that protect against pollution of the environment and in effect regulate development, to other departments of the county government.

These proposals and actions have been made in the name of "efficiency," "economy," "the streamlining of county government" and "making county government more responsive to the people."

Other proposals have been made that would consolidate the county health department, after elimination of the board of health and the health director, in a Department of Human Services. "Public Health" as an entity would disappear as its personnel and activities would be grouped, together with those of "other welfare agencies" and the whole placed under a politically appointed lay administrator.

These are reasons why the North Carolina Medical Society has come to the defense of the state's local boards of health. These are the key elements in the system of environmental protection and other public health measures that the Society itself pioneered in 1877. Now, over a century later the Society again has initiated actions designed primarily to prevent the pollution of water supplies, but also to protect against other environmental hazards.

At the suggestion of the Wake County Medical Society, which had taken the same step previously, the Society adopted a resolution supporting the repeal of N.C.G.S. 153A-77. Stating that " . . . organized medicine spawned public health in the State of North Carolina and has nurtured it throughout its history," the resolution continued by stating that "duly constituted statutory boards of health provide a reasoned, professional, informed buffer between

* House Bill 604 submitted to the General Assembly from Mecklenburg County.

the political pressures upon city councils and county commissions and the needs driven pressures upon the local public health agency'' and concluded by supporting repeal of this law that makes possible the elimination of boards of health. It then approved the transmittal of the Society's action to other professional societies and organizations along with encouragement for them to support repeal of this law, also.

Other professional organizations have taken similar actions at the county and at the state level.

The processes of communications and of coordination of efforts that were declared to be vital by the participants at the seminar in Atlanta have begun. They must continue and be expanded so that there will be the necessary coordination of efforts with other agencies, organizations and individuals with similar interests and goals, at the county and at the state levels.

It remains now for the physicians of the state, individually and as organization entities, to play the key role outlined for them at the Environmental Health Seminar in Atlanta. It is they who must educate and advocate.

This is necessary if our state is going to retain its local boards of health, health departments and qualified public health professionals, and if our health department personnel are going to be insulated from political, economic and developmental pressures as they work to protect our communities from water-borne and other environmental hazards.

We need to act as if our lives depend on it. They just might. So might those of our children and of their children, also.

From Dr. Axalla J. Hoole, an internist in Chapel Hill.

One can easily be misunderstood in making suggestions about ecology and the environment to a group (a county medical society) that might consider these issues tangential; for the term ecology brings out social and political emotions rather than medical ones. An activist for ecological issues is more likely to be thought a crazed member of a different political party or a socialist with anti-capitalist leanings than a physician who considers problems of the environment and ecology genuinely important to health and topics that should be considered by county health societies. I personally take the latter view, and feel that many of the medical problems we face in the future will be created by man's misuse of his environment. Physicians will be asked for opinions and solutions.

If I were to make a suggestion to a county medical society, I would use PSR (Physicians for Social Responsibility) as my model. This is a non-partisan group that has taken the position that nuclear war presents the greatest long-range threat to the health of mankind; though education PSR hopes to practice preventive medicine. Presentations by this group have been very important in debunking the myth that organized medicine can somehow ameliorate the results of a nuclear disaster; through presentations of many kinds they have helped people understand the medical consequences of nuclear war. I would suggest to a county medical society that in a similar way a few programs be set aside each year for presentations of environmental issues (acid rain, food additives, nuclear waste disposal — our potential for hurting ourselves is seemingly limitless) so that members of the society might consider the seriousness of the problem and consider appropriate responses as a group or as individuals.

It is clear that the famine in Africa has been brought about in part by ecological abuses — overpopulation, overgrazing of pastures, changes in agricultural practices; the response of organized medical care in a traditional sense is now almost irrelevant. When would it have been appropriate for physicians to accept the consequences of these abuses as health problems, and through education and understanding sought to intervene?

From Dr. Morris A. Lipton, a psychiatrist in Chapel Hill.

In the 200 years since the Industrial Revolution, man has changed the earth more than all other species since the beginning of life several billion years ago. Man's population quadrupled and continues to grow rapidly. Man's immediate needs for food, energy and manufactured goods and the profits derived from generating and distributing them are so great that we tend to ignore their longer range consequences. Thus, we tolerate the depletion of natural resources such as forests and soil and the pollution of our soil, water, and atmosphere. The earth's size and resources are so great that the effects of deterioration are insidious rather than dramatic. In contrast with the immediate benefits from such exploitation, apprehension about longer range detriments often loses out.

Individual maturation always involves learning how to postpone immediate gratification for the sake of longer range benefits. We do this when we invest years in education or when we protect our families with insurance. Yet, many prudent people (patients and doctors alike) smoke, drink, overeat, abuse drugs and indulge in serious risk taking behavior at work or at home. In each case the immediate consequences are gratifying while the longer range ones seem improbable, even though they may be deadly when they occur. This paradox exists in all of us. Live for today, but plan for the future.

Socially we may be even less mature than we are individually. In order to maintain our living standard and to compete with other nations, we cut corners in industrial safety and in the disposal of toxic wastes while we simultaneously deplete and poison our beautiful land. The ultimate absurdity is demonstrable in the nuclear energy industry where for the sake of cheap electricity we engage in producing fissional by-products we do not know how to dispose of safely. Needless to say we are also producing nuclear weapons whose use in war will so badly pollute the environment with radionuclides and soot generated by the burning of cities that civilization as we know it and perhaps life itself will become extinct.

American medicine is in a tumultuous state. On the one hand, it is becoming more industrialized and dependent upon high technology. On the other hand, it is increasingly concerned with health promotion and disease prevention rather than the ''fix it'' medicine which has been our preoccupation for so long. Health promotion and disease prevention require vigilant concern for the deteriorating

and dangerous environment in which we all live. The modern physician is broadly trained in the natural, biological and behavioral sciences. Moreover he encounters daily the pain and death that is associated with indulgence and abuse of the self or the environment. Like everyone else he has the need for daily gratification and must endure some daily frustration. Nonetheless, he is equipped professionally to understand the problems of maintaining a healthy environment and ecological balance. Properly he should take active leadership in considering these matters.

From Dr. Charles I. Sheaffer, a pediatrician in Chapel Hill.

I think this is an interesting question and have not previously given much thought to it. Perhaps an open statement encouraging programs such as those sponsored by North Carolina Wildlife Federation, perhaps encouraging school projects, and perhaps giving an award to the grade school which gives the most innovative approach to ecology and pollution. In summary, I would favor supporting and giving credit to individuals who are approaching ecology and pollution reasonably.

• EDITOR'S NOTE:

I have always been curious about how we view the difference between the public's health and the health of a single individual. They seem to be intimately related but we have tended to split them. Expertise in the two areas requires different training. Physicians get to be pretty good in dealing with individual health but don't feel as expert when it comes to dealing with the public's health. If our Forum's writers are correct, we need to blur the margins between public and private health and become expert at both. The issues are too important to ignore.

For the next Forum question I would like to hear your opinions on a different issue. **Plumbers and electricians are paid for their services by the hour in a perfectly acceptable fashion. Should doctors also be paid for time spent with patients? If so, should this be controlled?** Please send your response by June 21 to Eugene W. Linfors, M.D., Box 3381, Duke University Medical Center, Durham 27710.

Terminal Illness Management Electives — The Establishment of a TIME Committee

Charles A. Speas Phillips, M.D.

• *The role of a TIME committee in the living of your last days.*

Fear of Death

For the majority of people, the fear of death[1] is less terrifying than the fear of the way in which one dies. Religion may provide relief from the fear of death, but the events that precede death will remain unknown until their occurrence. Will death be sudden? due to a heart attack? a paralyzing stroke? Or will death come slowly? be due to cancer? be prolonged, painful, expensive, and deplete family resources?

Decisions concerning death tax the healthy mind. Good decisions may escape the mind burdened with pain, agony, concern about loved ones to be left behind, or a body suffering indignities of tubes, catheters, pulmonary ventilators, etc.

It is therefore important to have a plan for this period,[2] as outlined in a "living will"[3] or thru a proxy[4] designated to make decisions. Good decisions will be made most frequently when accurate, current, and full knowledge is available. Patients, families, and frequently physicians need help — information and moral support — in arriving at the best decision, one that is most appropriate for the period of terminal illness, and one that will leave little guilt feeling thereafter.

Physician, family and/or patient rarely gain from "protection from the truth."[5, 6] The risk of withholding facts of diagnosis, prognosis and treatment alternatives from the patient is great for it denies the patient the autonomy which is rightfully his/hers. Paternalistic decision-making by physicians is fortunately declining rapidly. When obtainable, informed, competent, patient consent is considered essential, or in the absence of competence, informed family or other appropriate consent.

Making the Decisions

Competent adult patients should be free to make decisions after obtaining adequate knowledge from their physician, consultants and other sources of accurate and timely information. The patient's wishes for the future when he/she may become incompetent can be accomplished, at least in part, through a "living will" or by appointing a proxy. Many states have statutes which recognize "living wills." Certainly, written witnessed statements provide better protection than verbal expressions.

From Pinehurst Professional Center, 165 Page Road, Pinehurst 28374.

For those who have passed into incompetence, or for children who are not of age, state statutes, judicials decisions, and legal opinions[7] provide guidance as to who should make the decisions for, or withholding of, diagnostic tests, drugs, treatments, or surgery.

Decision makers (patients, parents, proxies, legal guardians, next of kin, etc.) should be free to exercise their responsibility with their physician *without* interference from government, "do gooders" or courts. Outside interference has been reported frequently as in the case of Quinlan,[8] "Baby Doe"[9] and others.

The position of the AMA, opposing government participation in the responsible party-physician relationship, was made clear in a statement issued in April 1983.[10]

The responsibilities of physicians to the terminally ill are well known and were reviewed recently by a group of renowned physicians.[4]

Jackson and Younger[11] have pointed out some clinical situations in which precautions must be used to avoid pre-empting the patient's right to make decisions.

Some Problems of Concern to the Terminally Ill and Their Families

Some principal concerns to be addressed in the terminal period are:

1. *Seeking the "needle in the haystack"* — wandering elsewhere looking for promise of a cure after the family physician has honestly informed the competent patient and/or family that there is little hope of cure or improvement.
2. *Prolongation of agony* — continuing the use of diagnostic tests and treatments that offer little or no chance of improving the quality of life or reversing the course of the terminal illness.
3. *Relief of pain*[12] — when the finality has been identified, withholding of pain relief has no place in medicine, even with danger of addiction.
4. *Indignities* — continued use of IVs, tube feeding, gastrostomies, pacemakers, catheters, etc., which prolong and may increase agony and suffering should be assessed to evaluate improvement in the quality of life they may provide.
5. *Wiping out of family resources* — understood, the patient's welfare is paramount. Yet how often have useless treatments been carried out without offering the patient improvement in quality or significant prolongation of life,

only to wipe out family resources, often to the point where the family exists at poverty levels or education is denied the children?

How to Help the Patient. The TIME Committee[13-16]

The hospital in its bylaws should establish a TIME committee. The word TIME is the acronym for *T*erminal *I*llness *M*anagement *E*lectives. This patient service committee establishes policies and resources for the optimum care of hopelessly ill patients. It is composed of interested persons from the community, a variety of physicians — family physician, surgeon, oncologist, radiation therapist — floor nurse, clergyman, lawyer, social worker, and representatives from home care agencies and hospices. The TIME committee identifies interested persons and defines policy and procedures which provide information and moral support. The members of the committee are a resource for the patient and family and physicians who need information and moral support.

The TIME committee should establish ways for persons on the staff to be available to:

1. Assess family problems and concerns, resources, goals and patient competence.
2. Assimilate various alternatives for the patient and family.
3. Counsel with the patient and family to provide information on diagnostic procedures, treatment modalities and procedures such as chemotherapy, irradiation therapy, surgery, resuscitation[17] or not, and levels of treatment facilities such as acute care, skilled nursing care, long term care, rest home, home care, and/or hospice care.
4. Establish policies for administration of "living wills" or use of a designated proxy.
5. Establish reasonable criteria for withholding treatment including resuscitation — DNR[18] (Do Not Resuscitate). Such criteria would include at least an established diagnosis for a fatal illness which is in a terminal and irreversible state such as coma.[19] A written DNR policy should be developed and have hospital staff approval.
6. Additional responsibilities might include the education of patient and staff concerning applicable laws and policies that relate to assessment of competence, definition of death, guidelines for procurement of organ donors, and guidelines for harvesting organs for transplant.

Patients, families, and physicians are most likely to make the best decisions in the period surrounding death with full knowledge of diagnosis, treatment alternatives, and prognosis. The estabishment of TIME committees is encouraged to develop policies and procedures for assistance through information and moral support to those persons making difficult decisions.

The exact role of technology, compassion, sanctity of life or quality of life,[20] access to care, resources available, and legal precedents change rapidly with time, but with experience and knowledge, we may arrive at a point in the future when we may look forward to comfort and dignity and freedom from fear and pain during our last days.

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Medical Revolution — Hospital Crisis

John F. Lynch, M.D.

• *The Chairman of the North Carolina Medical Care Commission updates us on medical and hospital progress in recent years.*

CONTROL of large segments of infectious disease, fantastic strides in public health (clean water, pasteurized milk, sewage disposal, etc.), nutritional successes, development of specific treatments for many diseases — these are a few of medicine's achievements in the last hundred years. They have allowed us to enjoy an unheard of degree of comfort, security, and good health.

This medical revolution has been accomplished through a vast effort by our whole society. In North Carolina our public sector has joined in this effort through hospital programs and unlimited support.

In the 1940s, a "Good Health" program was conceived and successfully initiated our present hospital program. Mr. Kay Kyser spearheaded the effort. We did not have hospitals that were adequate. Our goal was hospitals in every community where one could be supported. Our basic guideline was four hospital beds per 1,000 population. Since that campaign, over 40 years ago, these objectives have been largely accomplished.

The hospitals of that day were not very sophisticated. Most of today's ultramodern technology was unknown.

Progress has radically changed the above concept. World War II diminished the length of hospital stay. We found it was not necessary to keep sick people in bed for long periods. We found that they did better if they got up sooner, and bed rest has continued to shrink as a necessary part of convalescence. Gradually a great variety of factors altered the balance between hospital care and ambulatory care. Not only did the length of hospital stay shorten but the number of hospital days per 1,000 persons decreased.

Other marks of progress:

Medical:

1. Better medical and drug treatment of disease.
2. Better surgical techniques and pre- and postoperative care.
3. Day surgery (in California, as much as 60% of surgery is day surgery; in North Carolina 30%).
4. Development of intensive care units (CCU, ICU, intensive care nurseries).
5. Emergency room coverage (full-time).
6. Emergency medical service with transportation: ambulances, helicopters (one of our great strides).
7. New diagnostic and treatment techniques — invasive and non-invasive (CAT scanners, radiology, mechanized laboratory, etc.).
8. Surgicenters.
9. Birth centers.
10. Urgent care centers.
11. The pill.
12. Legalized abortion with abortion centers.
13. Preventive care programs, as in daily public health activity.
14. Better care of aging population, nursing homes, life care centers, and so on.
15. Transplantation of hearts, lungs, livers, and kidneys.
16. Mechanical hearts for temporary support and for long-term support.

Economic and Political:

1. Decreasing coverage for in-hospital patient care from medical insurance, government programs, and corporate medical benefits.
2. HMO, PPO, etc.
3. Inflation with huge increase in cost.
4. Technological advances with demand for ultimate care for every patient.
5. Increased standard of education and living.
6. Entitlement programs.

With these and many other factors, hospital usage continues to go down. Modern technology and advances have greatly increased the use rate of hospitals; this is more true in full service hospitals than smaller ones, but length of stay has diminished unbelievably. The services now given in the hospital are more expensive and more sophisticated. North Carolina faces quite a dilemma. We have 26,000 general hospital beds. Currently on any day of the year almost 10,000 are empty. Hospital bed occupancy in North Carolina went down 10% in 1982 and 10% in 1983. It probably went down equally as much in 1984.

With all these events and facts, it is not much of a mental exercise to see what is happening to hospital usage. Also in North Carolina we have several hospitals (currently breathing their last) with practically no patients, and they are approaching bankruptcy. In addition we have a number more with a patient census so low they cannot justify staying open and generally are in deep financial trouble. Hospital financing today is a universal problem.

This is a critical problem and demands good common sense solutions.

As is obvious, the old small general hospital in every

From 905 Arbordale Drive, High Point 27260.

community no longer fits the medical needs of our population. Since World War II, the character of hospitals has changed. Generally, a hospital was a hospital. In reality, a 50-bed hospital was a miniature medical center. In other words, all hospitals, with some exceptions of course, did essentially the same thing. This has changed drastically and we can now identify distinct levels of service that various categories of hospitals provide.

Perhaps it should be pointed out that the closing of beds in small, financially troubled hospitals may not be the worst thing in the world that could happen. Rather than have an underfinanced, understaffed, behind-the-times hospital, a community could use its resources to better advantage by developing alternatives to hospitalization. Such things as urgent care, convalescent care (nursing homes), group practice, ambulatory surgery, rural health clinics and a good medical transportation system are suggested. Leave the heavy stuff to well established hospitals. The more sparsely populated areas may be able to develop excellent alternatives but not afford a full-blown hospital.

This is going to be traumatic and will demand everyone's best efforts. People must work together who never have before. Hospitals are usually one of a community's biggest industries, with a large number of employees. Hospitals are a source of great civic and political concern and pride. Like schools, medical care is considered when relative desirability as a place to live is evaluated. Truly, these decisions are going to take all our mutual understanding and cooperation as well as love and compassion.

As if this were not enough, the "medicine revolution" is just beginning. In our immediate future we will see changes the average person can barely comprehend, but they are here.

Soon, many hereditary diseases will be corrected or prevented by genetic engineering. Cancer will be cured by early diagnosis and early treatment with techniques being developed, one of which the media have termed the "silver bullet." All mental disease will be treated medically. Preventive medicine will vastly improve.

We will regularly do a mini-physical examination for ourselves at our breakfast table, with our personal computers, then have an answer per computer. Here we can each morning do our own urinalysis, blood pressure, many chemical analyses (blood sugar, cholesterol, etc.) and test for many different early forms of cancer.

Yes! The revolution has barely begun. It is fantastic and exciting. It is going to take the best of all of us.

The medical profession, as represented by the North Carolina Medical Society, and many allied sciences, as well as all of society should not be bashful. They should all stand up and take a gracious bow. Then we must all lend our best efforts to correcting the rough spots as these great new programs and improvements in life evolve.

The following letter, sent to new members of the North Carolina Medical Care Commission by its Secretary, explains the role and activities of the Commission.

Governor Martin's office has advised us of your appointment to The North Carolina Medical Care Commission and has asked that you be furnished information regarding the Commission's activities.

The Medical Care Commission was created largely as a result of a finding of a special commission, the North Carolina Hospital and Medical Care Commission. This Commission was appointed in 1944 by Governor Broughton to study the critical shortages in general hospital facilities and trained medical personnel in the State, and to make recommendations for improvements in these areas. Among recommendations which were made was a proposal that the legislature provide for a permanent state agency responsible for the maintenance of high standards in North Carolina's hospitals, administering a medical student loan fund, and a statewide hospital and medical care program.

When the 1945 General Assembly established the Medical Care Commission, it followed closely the proposals of the North Carolina Hospital and Medical Care Commission. Enabling legislation authorized the Commission to:

1. Make a survey of the hospital resources in the State and to formulate a statewide program for construction and maintenance of local hospitals, health centers and related facilities, and to receive and administer Federal and State funds appropriated for such purposes.
2. Make loans to students who wish to become physicians.
3. Survey all factors involved in the location of the expanded University Medical School. (The same act authorized the expansion of the UNC Medical School from a two-year to a four-year school.)
4. Several other activities which are not now included in the Commission's responsibilities.

In writing this enabling legislation, the General Assembly accurately anticipated the Federal legislation that was to come a year later. In 1946, Congress passed the Hill-Burton Act and the Medical Care Commission met all Federal requirements and was designated as the state agency authorized to administer the program within North Carolina. Since 1946, health facility construction in North Carolina under the Hill-Burton program has totaled more than $500 million, of which 40% was financed with Federal funds; 5%, State; and 55% local. Of the more than 500 Hill-Burton projects, 241 were general hospital projects, including 80 all-new facilities. As you may know, the Hill-Burton program was incorporated into the National Health Planning and Resources Development Act of 1974. Since that time, Congress has not appropriated additional funds for construction.

Since passage of the Executive Organization Act of 1973, The North Carolina Medical Care Commission has functioned under the Department of Human Resources and consists of 17 members. Three are nominated by the State Medical Society, one by the State Pharmaceutical Association, one by the North Carolina State Nurses' Association, one by the North Carolina Hospital Association, and one by The Duke Endowment. These nominations are subject to approval of the Governor. In addition, 10 members, one of whom by law must be a dentist, are appointed by the

Governor.

Today the Commission is responsible for the governance of eight programs:

1. the licensure of hospitals;
2. licensure of outpatient surgical facilities;
3. licensure of nursing homes;
4. licensure of home health agencies;
5. licensure of hospices;
6. the regulation of ambulances and emergency medical services personnel;
7. the issuance of revenue bonds for the construction of hospitals and related facilities;
8. certification of freestanding abortion clinics.

The 1975 session of the General Assembly enacted the Health Care Facilities Finance Act (G.S. 131A) which authorized the Medical Care Commission to issue its tax-exempt revenue bonds and to lend proceeds from the sale to finance construction projects. To become eligible for tax-exempt status, a hospital must deed all properties affected by the project to the Commission. After financing, the Commission may lease the facility to the hospital for operation, sell the facility back to the hospital or accept a mortgage on the property. In any event, the hospital regains title to the properties after the bonds are retired.

Under this program, the Commission has authorized approximately $335 million for construction projects. In addition, projects amounting to more than $230 million are in the planning process. The Facilities Finance Act has become the major vehicle for obtaining capital funds for nonprofit institutions.

In 1973, the General Assembly passed the Emergency Medical Services Act of 1973 which greatly expanded the responsibility of State Government in the area of EMS. This act vests responsibility for the development of a comprehensive program in the Secretary of Human Resources and authorizes the creation of a statewide EMS program. This legislation reaffirms the State's regulatory role by requiring inspections of ambulances, the issuance of permits for the operation of ambulance vehicles, and the certification of ambulance personnel. Authority was given to the Medical Care Commission to promulgate rules and regulations necessary to carry out the governance of ambulance services.

The Commission regularly meets the third Friday of the last month of each quarter. The next meeting is scheduled for June 21. An Executive Committee meeting is usually held on Thursday evening prior to the Commission meeting of Friday morning. All members are reimbursed for travel expenses and subsistence subject to the limitations prescribed by G. S. 138.5. In addition, a per diem payment is made in the amount of $15.00.

Names and Addresses of Current Members of the Commission

Members	Address	Original Appointment	Term Expires
John F. Lynch, Jr., M.D., Chairman	905 Arbordale Road High Point (27262)	1972	June 30, 1987
Thomas R. Howerton, Vice-Chairman	The Program on Access to Health Care P. O. Box 10937 Raleigh (27605)	1965	June 30, 1988
Gwendolyn Blount	1224 Eastside Drive Greensboro (27406)	1984	June 30, 1986
Jack L. Church, M.D.	942 Norwood Street Lenoir (28645)	1982	June 30, 1986
Jack V. Hill, D.V.M.	2126 Hope Mills Road Fayetteville (28304)	1977	June 30, 1985
James A. Johnson, M.D.	P. O. Box 5708 High Point (27262)	1977	June 30, 1985
David A. Jones	2054 Cynthia Drive Mount Airy (27030)	1980	June 30, 1988
Billy G. McCall	The Duke Endowment 200 S. Tryon Street, Suite 1100 Charlotte (28202)	1977	June 30, 1985
Daniel D. Mosca	Hillhaven Regional Office 3801 Old Wake Forest Road Raleigh (27609)	1983	June 30, 1987
Tom Paxton Phillips	3101 Sharon View Road Charlotte (28210)	1980	June 30, 1987
Mary Edith Rogers	1264 Queensgate Gastonia (28052)	1978	June 30, 1986
W. Lewis Sauls	Courthouse Square Whiteville (28472)	1984	June 30, 1985
O. R. Stovall, D.D.S.	304 Bunche Drive Goldsboro (27530)	1980	June 30, 1987
Kathy Arnold Taft	611 Queen Anne's Road Greenville (27834)	1984	June 30, 1988
David T. Tayloe, M.D.	608 East Twelfth Street Washington (27889)	1973	June 30, 1985
William H. Wilson	2000 Fairview Road Raleigh (27608)	1974	June 30, 1986
Louie E. Woodbury, Jr.	Post Office Box 270 Wilmington, N. C. 28402	1984	June 30, 1988

Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

June 19

Cutaneous Manifestations of Systemic Illness
Place: Sanford
Credit: 2 hours Category I AMA
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

June 20

Crisis — Then & Now
Place: Elizabeth City
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

June 23-28

NC Health Promotion Wellness Institute
Place: Raleigh
Credit: 27 hours Category I AMA, AAFP
Fee: $260-370
Info: Jacqueline Rollins, Wake AHEC, 3000 New Bern Avenue, Raleigh 27610. 919/755-8018

July 5-7

15th Annual Sports Medicine Symposium
Place: Wrightsville Beach
Info: Alan Skipper, NCMS, Box 27167, Raleigh 27611. 919/833-3836

July 11

Crisis — Then & Now
Place: Hickory
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 15-19

Sonography of the Abdomen
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: Dianne L. Willard, Bowman Gray, Winston-Salem 27103. 919/748-4505

July 16

Crisis — Then & Now
Place: Wilson
Info: Wayne Parker, MMIC, Box 27444, Raleigh 27611. 1/800/662-7917

July 17

Diabetes/New Care Concepts
Place: Sanford
Info: Robert S. Cline, M.D., Central Carolina Hospital, Sanford 27330. 919/774-6518

July 29-August 3

Diagnostic Imaging
Place: Atlantic Beach
Fee: $350
Credit: 18 hours Category I AMA
Info: Carl E. Ravin, M.D., Box 3808, Duke University Medical Center, Durham 27710. 919/681-5268

OUT OF STATE

June 27-29

Bones, Joints, and Sports Injuries
Place: Virginia Beach, VA
Fee: $275
Info: Beth Winn, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

July 1-6

Mid-Summer Family Practice Digest
Place: Myrtle Beach, SC
Fee: $300
Credit: 30 hours AAFP
Info: NCAFP, Box 20146, Raleigh 27619.

July 19-21

5th Annual MCV Cardiology Conference
Place: Hot Springs, VA
Fee: $275
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

New Members

ALAMANCE-CASWELL

Wayne Kimberly Ruth (PUD), 327 Graham-Hopedale Road, Burlington 27215

BEAUFORT-HYDE-MARTIN-WASHINGTON-TYRRELL

Edward Feldin Hill (FP), 501 W. 15th St., Washington 27889

BUNCOMBE

Harry G. Burton, III (CDS), 17 Brookside Road, Asheville 28803

BURKE

William Townsend Freeman (AN), P.O. Box 2245, Morganton 28655

CUMBERLAND

Norman Irwin Snyder, 3425 Melrose Road, Fayetteville 28304

Douglas Wayne Whetsell (IM), 1756 Metromedical Dr., Fayetteville 28304

DURHAM-ORANGE

Carl Elving Anderson (Resident), 1702 Vista St., Durham 27701

Abdullah Onsy Askar (Resident), 2748 Middleton Ave. 15-H, Durham 27705

Gregor George Cleveland (Student), 114-A High Street, Carrboro 27510

Elizabeth Jane Engelhardt (student), 418 Ridgefield Road, Chapel Hill 27514

Hratchia Havoundjian (student), 4545 S. Chelsea Lane, Bethesda 20874

Hector Jesus Hidalgo (DR), 2609 N. Duke St., Durham 27704

Victor Wei Ho (student), 801-B Watts St., Durham 27701

Bettina Bass Meekins (resident), 6 Saint James Court, Durham 27713

Herbert Charles Pfaff (student), 1204 N. Gregson St., Durham 27701

James Scott Rankin (CDS), Box 3851, DUMC, Durham 27710

Bennie Dwayne Roberts (student), 1119 Hillcrest Dr., Chapel Hill 27514

Marc Scott Schwartzberg (student), 6-A Estes Park Apts., Carrboro 27510
Kassell Eugene Sykes, Jr. (student), G-11 Estes Park Apts., 306 Estes Dr., Carrboro 27510
Jo Marlene Travis (student), 1340-5 Ephesus Church Rd., Chapel Hill 27514

EDGECOMBE
Steven Seth Leblang (FP), P.O. Box 688, Pinetops 27864

FORSYTH-STOKES-DAVIE
David Craig Apple (student), 624 Westend Blvd., Apt. #5, Winston-Salem 27101
Dewey Herbert Bridger, III (student), 2518 Weymouth Road, Winston-Salem 27103
Steven Ping Chan (student), Medical Student Box 91, Bowman Gray Medical School, Winston-Salem 27103
Toni Michele Cutson (FP), 8838 Homewood Drive, Clemmons 27012
Andrew Martin Davey (student), 1618 Queen St., Winston-Salem 27103
Kenneth Robert Francis (student), 2353 Salem Court-D, Winston-Salem 27103
Fairfield Goodale (PTH), 300 S. Hawthorne Road, Winston-Salem 27103
Joseph Scott Greene (student), 236 Lockland Ave., Winston-Salem 27103
Kelley Ann Heller (student), 2250 Sunderland Rd., Apt. 19B, Winston-Salem 27103
Bonnie Jean Kerr (student), Box 245, Bowman Gray, 300 S. Hawthorne Road, Winston-Salem 27103
Ernest Paul Phillips, Jr. (CD), 1405 Plaza Drive, Winston-Salem 27103
Lea Harding Rayman (student), 1840 Elizabeth Ave., Winston-Salem 27103
Anthony Richard Riela (resident), 4300 Mill Creek Road, Winston-Salem 27106

GASTON
Karl Joseph Schmitter (GS), 902 Cox Rd., Ste. 6, Gastonia 28054

GUILFORD
Donald Joe Digby (OPH), 3312 Battleground Ave., Greensboro 27410
Salvatore John Pelligra (PM), 3033-B Pisgah Place, Greensboro 27408

IREDELL
Michael Avery Kepley (OBG), 750-H Hartness Rd., Statesville 28677

JOHNSTON
John Francis Ivan Zeedick (AN), P.O. Box 1950, Smithfield 27577

MCDOWELL
Lawrence Stanley Rosen (U), Route #1, Box 2312, Old Fort 28762

MECKLENBURG
Danny Edward Huntley (FP), 7128-B Albemarle Road, Charlotte 28212
John Peter Santamaria (resident), 1540 Garden Terrace, Apt. 208, Charlotte 28203
James Neil Shearer, 2711 Randolph Rd. Ste. 507, Charlotte 28207

MOORE
Thomas Raymond Kearney (P), 140 S.W. Broad St., Box 56, Southern Pines 28387

NEW HANOVER-PENDER
Kenneth Marburg, 343 Bradley Dr., Wilmington 28403
John Lauren Remington (R), 2101 S. Live Oak Parkway, Wilmington 28403

ONSLOW
George Henry Reichling (D), 224 Memorial Dr., Jacksonville 28540
Pirkko Esteri Reichling (GP), 224 Memorial Dr., Jacksonville 28540

PITT
Jennifer Anne Coats (student), 2603 Crockett Dr., Greenville 27834
John Frederick Holter (IM), Highway 64 West, P.O. Box 310, Bethel 27812
Christopher Jones (student), #4 Wildwood Villas, Greenville 27834
William Paul Lavietes (student), 1809 E. Fifth St., #14, Greenville 27834
Winslow Britt Melvin (student), 108 N. Elm St., Greenville 27834
Walter James Metzger (Al), Dept. of Medicine, ECU School of Medicine, Greenville 27834
Zane Thomas Walsh, Jr. (student), 106 Greenway Apts., Greenville 27834
Bruce Wilhelmsen (ORS), 117 Medical Drive, Greenville 27834

RANDOLPH
Edward Decker Haak, Jr. (IM), 208 Foust St., P.O. Box 2839, Asheboro 27203

ROCKINGHAM
Ayyaz Mahmood Qureshi (IM), 505 N. Third Ave., Mayodan 27027

RUTHERFORD
John Jefferson Carter, Jr. (P), City Rt. #3, 311 Fairground Rd., Spindale 28160

WAKE
George Sadler Edwards, Jr. (ORS), 3410 Executive Dr., Raleigh 27609
Linda Chappell Mohr (OBG), 1100 Dresser Court, Raleigh 27609

WAYNE
James Norman Atkins (HEM), 201 Cox Boulevard, Goldsboro 27530
Thomas Marvin Knutson (EM), P.O. Box 10867, Goldsboro 27530

Letters to the Editor

More on Tails of Woe

To the Editor:

Dr. Frazier's scientific article, "Coccydynia: A Tail of Woe," (NCMJ 1985;46:209-212) is a very well written, interesting and informative paper. I congratulate her. The four illustrative cases were well selected and are most appropriate.

Having seen and treated several hundred people with this disorder, I have had some interest in it. The mechanical variations and the mechanical aspects of the condition pointed out by Dr. Frazier in her publication need further clarification. The recommended treatment in most of her cases was a foam rubber donut and/or a U-shaped pillow.

I have found that a much better form of treatment is to explain to the patient the nature of this mechanical (and only secondarily inflammatory) problem. As Dr. Frazier mentioned, the abnormal mechanical stress on the sacrococcygeal joint can be removed by having the patient sit up straight so that their body weight rests on their ischial tuberosities and their posterior thighs. This can be achieved by having the person sit on a *firm* seat which is not too low and, most importantly of all, to keep their buttocks in the posteriormost portion of the chair — that is, to keep their buttocks up against the back of the chair.

I feel that the sponge rubber donut and U-shaped pads should be outlawed. The hysteroid patients that were mentioned in Dr. Frazier's article do take this as a "badge" and sometimes use this as a crutch for years. Another category, such as case three, is embarrassed by carrying around a pillow to sit on. The pillow, in itself, does not relieve the mechanical stress. The mechanical stress can just as easily, or more easily, be relieved by proper sitting posture (with the buttocks posteriorly against the seat).

Paradoxically, soft seats are worse than hard seats. If one sits improperly on a hard seat there is discomfort at the time (such as sitting on a hard athletic stadium seat). This discomfort then warns the patients and they have a tendency then to sit more properly. Conversely, if one sits on a low seat, such as on a soft couch, the body's warning system is delinquent in this anatomical area and oftentimes the persons don't have discomfort until some hours later.

Approximately 5% of the several hundred patients that I have seen have been patients who had had a coccygectomy and are still having symptoms. These patients will respond to proper sitting posture, just as will those who have not been operated upon. Conversely, having the surgery and continuing to sit improperly oftentimes does not relieve patients of their symptoms. I have never operated for coccydynia.

Dr. Frazier's point that an appropriate history and physical are necessary needs emphasizing. The pathological processes, such as in case number four, which were proximal to the sacrococcygeal joint will not have the same history in that they will have discomfort at times other than when they are sitting (night pain) and oftentimes will have lower gastrointestinal or genitourinary tract symptoms. Fortunately, these causes of coccydynia are extremely rare.

Persons who use the sponge rubber donuts, etc., and aren't helped will usually then get in the habit of sitting with their weight primarily on one ischial tuberosity or the other. This then causes lumbosacral symptoms.

If a person follows instructions regarding proper sitting posture (with their buttocks against the posterior aspects of the chair and sitting forward so their weight rests on the ischial tuberosities and posterior thighs) they will be relieved of this mechanical discomfort of coccydynia. If persons are not relieved after having been sitting properly for a few weeks, the doctor must then look for some other cause of the discomfort.

Thomas B. Dameron, Jr., M.D.
P.O. Box 10707
Raleigh 27605

To the Editor:

I am grateful to Dr. Dameron for his observations on the treatment of coccydynia. The day that I received his letter we saw another patient with coccydynia. She was a 54-year-old librarian who thought she had "pulled a muscle" from frequent bending over. She had been collecting sea shells during a weekend at the beach and then developed pain "in the tailbone" which spontaneously improved over the next few days. It acutely worsened after riding a stationary bicycle in her exercise class. Her examination was normal except for exquisite pain on palpation of the tip of the coccyx.

We treated the patient by explaining the mechanical nature of the disorder: her coccyx is relatively unprotected because she is a thin woman. She probably traumatized her coccyx during the 3½ hour automobile ride to and from the beach and then she hurt it again sitting on the hard bicycle seat. Bending over to pick up shells was probably not related to the problem. Sitting all day as a librarian may have contributed further subacute coccyx trauma.

We gave instructions on proper erect seating posture and did not emphasize use of a doughnut or U-shaped pillow. As Dr. Dameron correctly pointed out, three of the patients in my article were not helped by a pillow even though the use of a pillow is unanimously recommended in the literature: Case I still has intermittent pain despite using a pillow at work for several years, Case III was not compliant and Case IV had progressive symptoms due to a tumor. Case II did improve while using a pillow during her most acute pain. Our most recent patient was relieved to hear the pathophysiology of coccydynia and felt that with proper seating posture she wouldn't need any further therapy. We'll see her in follow-up.

Linda M. Frazier, M.D.
Lovest T. Alexander, P.A.-C.
Department of Medicine
Duke University Medical Center
Durham 27710

Good Friday, 1985

To the Editor:

(Thank you, dear Lord, that you are in the "life-changing" business.)

A recent (Good Friday, 1985) visit to the tiny, but sparkling, Hope Mills home of Walter and Lille Mae Cain helped me to rediscover what is changing in my life. Walter (age 79) is now totally bedridden and aphasic, but has been lovingly cared for by his wife Lille Mae over the years. With admiration and wonderment, I remember telling Lille Mae in 1977 (when Walter was in the hospital with his last CVA) that "there is no way that you can manage him at home, short of becoming a trained nurse, and turning your house into a skilled nursing home."

Lille Mae smiles when we recall those words together, on one of my home visits (2-3 times per year) to check on another problem (decubitus ulcer, eye infection, bowel problem, bronchitis, etc.) that she has skillfully managed.

Walter is steadily failing, but his bedroom and their home are filled with life and joy, not death. Their life together is filled with the special love that shines through even the dark events of Good Friday.

"This is my commandment, that you love one another, as I have loved you" — John 15:12 *(RSV)*.

Thank you, Lille Mae and Walter, for showing forth this extraordinary love so clearly and forcefully, and sharing it with me.

Tom Woodworth, M.D.
1657 Owen Drive
Fayetteville 28304

Creation and Evolution

To the Editor:

Regarding "Thoughts on the Beliefs of Medical and Religious Institutions" (NCMJ 1985;46:29-32), I have heard from two other people. A physician in town (Greenville) told my daughter Susan that he liked the paper.

A physician in Siler City wrote and said he had read the paper. He invited me to attend a meeting on "Medicine and Society," to be held at the nearby high school and sponsored by the local medical society. I politely declined his invitation. However, it was good to know that the paper was not completely ignored.

I read Dr. Marion W. Griffin's letter to the editor, "Creation vs Evolution" in the February issue of NCMJ, and was amazed. The letter seemed an incongruous combination of correct facts and doubtful assumptions. I don't really know why I was shocked, since this sort of thing has happened often throughout history.

Anyway, his letter stimulated my writing a short article, called "Thoughts on Evolution and Creationism," which I am submitting for publication. I had to write this article; I could not concentrate on my book until I got this subject done with. If you decide to publish my article, and Dr. Griffin would like to reply to it, from my standpoint, he is welcome to do so. It might be a convenient way to halt the debate by allowing both sides to be presented in the same issue.

The editors of the NCMJ did a public service in publishing Dr. Griffin's letter. Far better to allow someone to blow off steam in the *North Carolina Medical Journal* than to start tampering with school textbooks and the education of the next generation.

Albert D. Warshauer,M.D.
1608 East Fifth Street
Greenville 27834

The Editor Replies:

Dear Dr. Warshauer:

As usual, I enjoyed your writing. The points are well taken and presented in an interesting fashion. Most of our audience will agree with your conclusions. You are preaching to the converted.

My suggestion is that you publish in a place where there are more creationists in the readership.

Keep in touch. You are never dull.

I will publish a portion of your letter and my reply.

Eugene A. Stead, Jr., M.D.
Box 3910, Duke Hospital
Durham 27710

STD Follow-Up

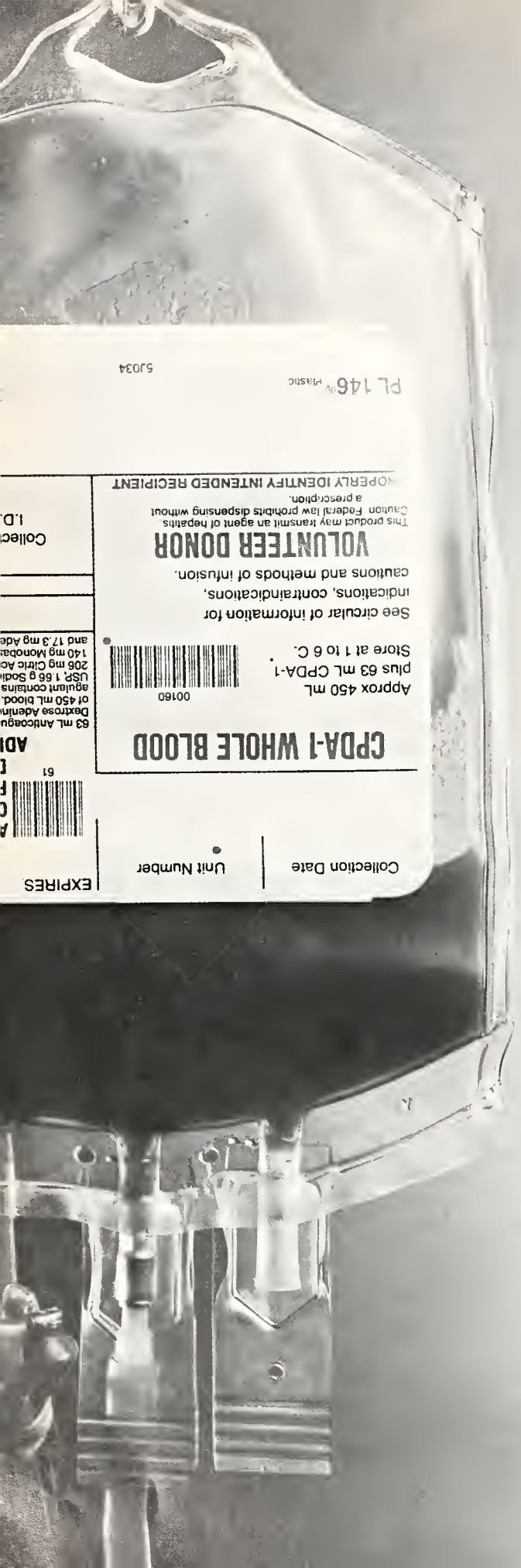
At the North Carolina Medical Society and Auxiliary Convention in early May, both groups recognized the serious epidemic problem of sexually transmitted diseases in North Carolina.

Much interest was generated and I had many inquiries about how a physician could add his/her name to the national referral listing. The VD National Hotline will provide clients who prefer private care and are able to afford it with a listing of private physicians on a fee-for-service, private-patient basis. It is desirable that physicians to whom patients are referred by the Hotline be those with a special interest and continuing education in STD — those for example, who subscribe to and read this journal.

To support this effort by adding your name to the national referral listing you can choose one of three approaches: (1) Call the Hotline Director, at 800-227-8922. (2) Since this line can be very busy, you can call the business number of the Hotline at 415-327-6465. (3) Send a note or post card containing your name, address of your practice, city, state, zip code, phone number, and county to Hotline Director, VD National Hotline, 260 Sheridan Avenue, Suite 307, Palo Alto, California 94306. The card or note should be titled "PMD Resource."

At this time of waning support for public efforts to control STD, the private sector must make a substantial contribution toward solving a health problem that affects so many.

Marguerite K. Tracy
138 Cherokee Road
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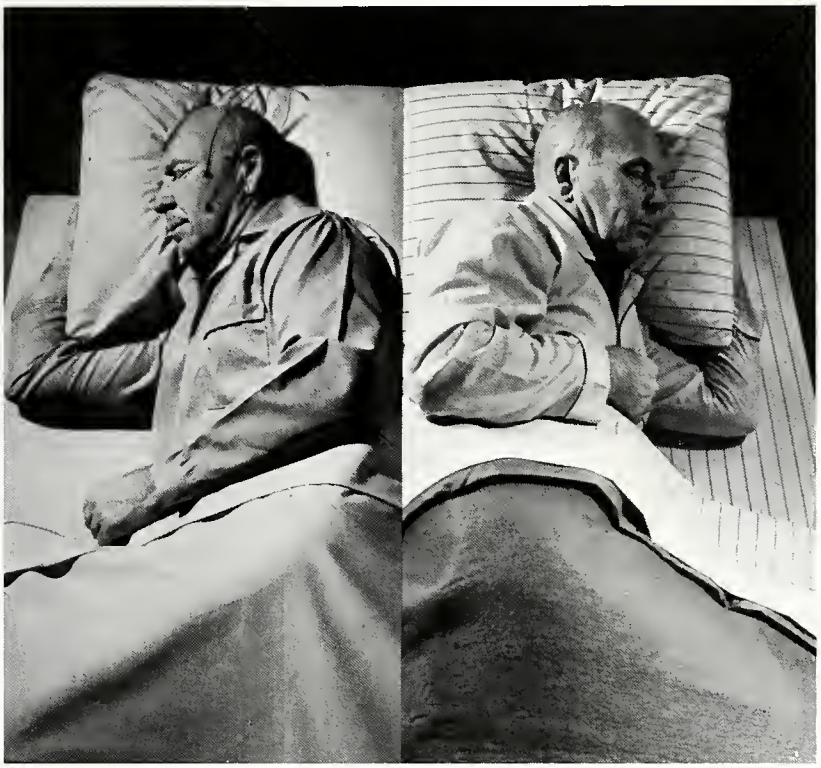
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References: 1. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res 9*(1):85-99, 1983. **10.** Monti JM: *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep 5*(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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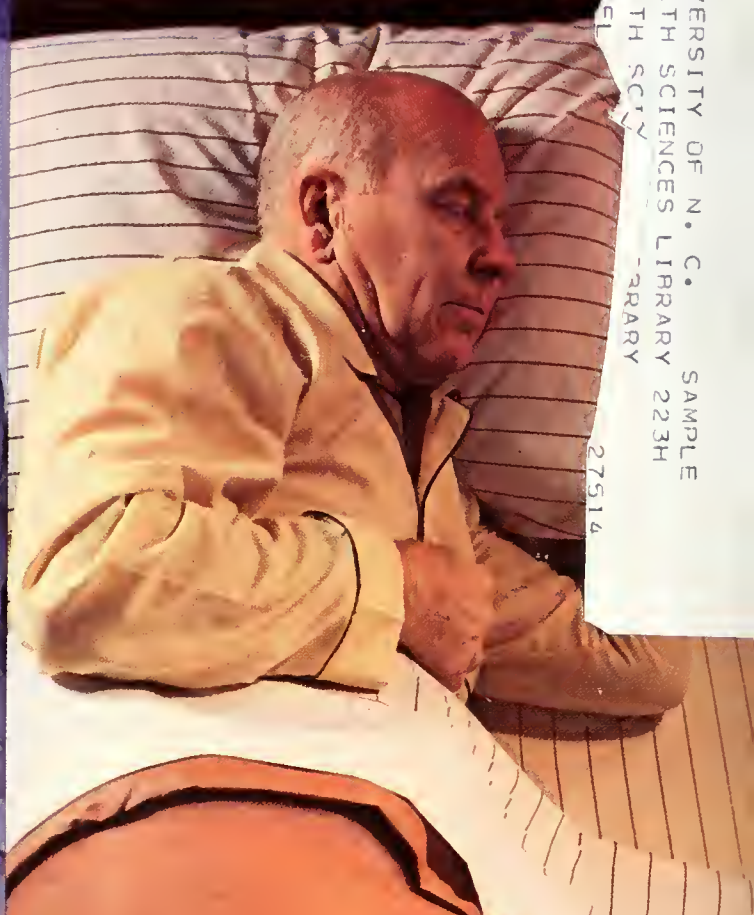
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